VOL. 34 OCTOBER 1958 NO. 10

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

SHIELDS WARREN

GEORGE K. SMELSER

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THERAPY OF COMMON ENDOCRINE DISORDERS

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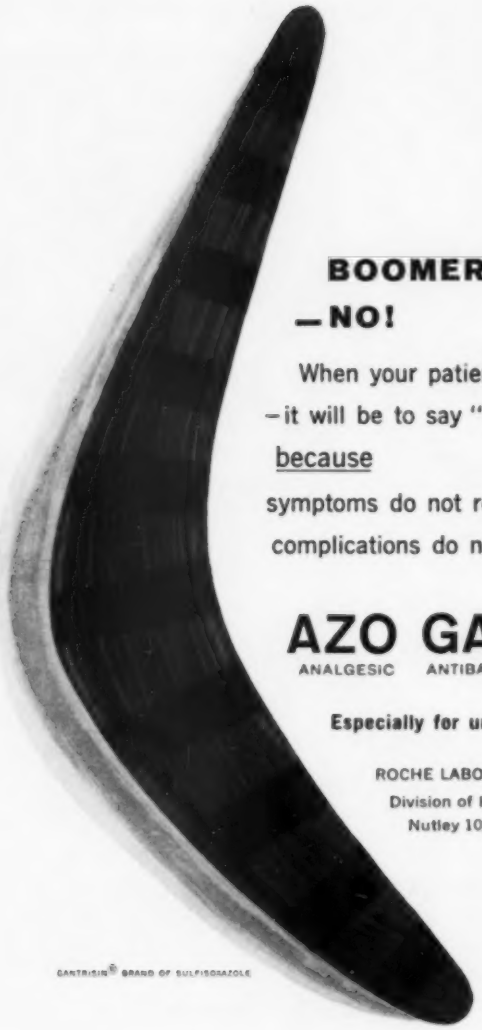

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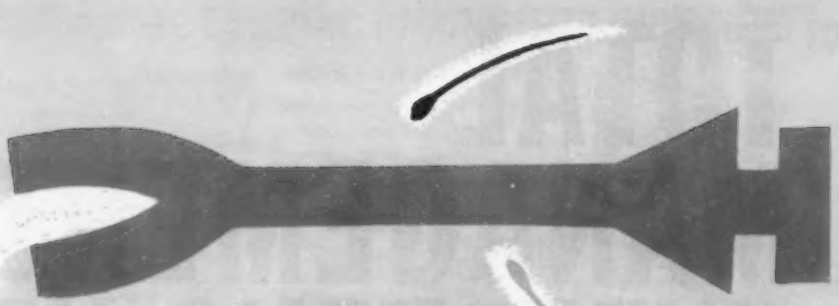

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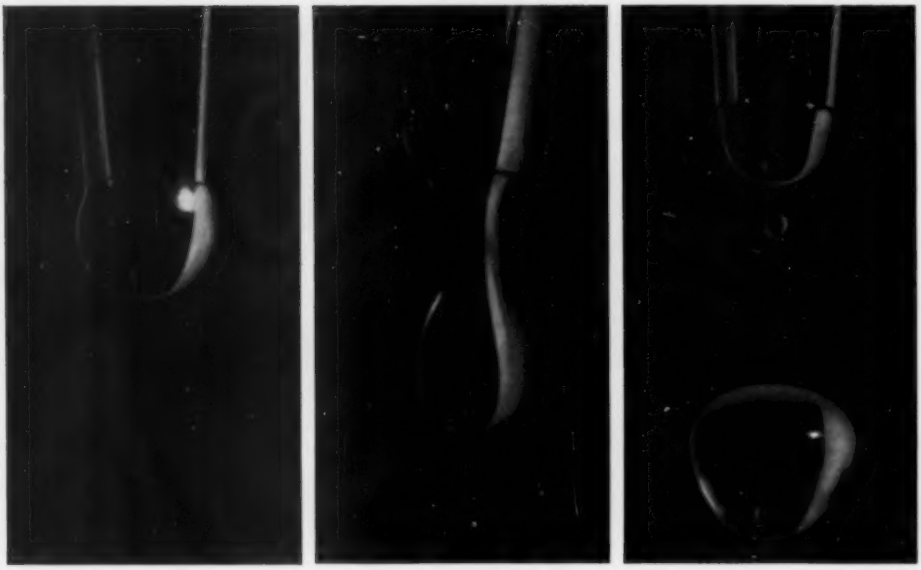

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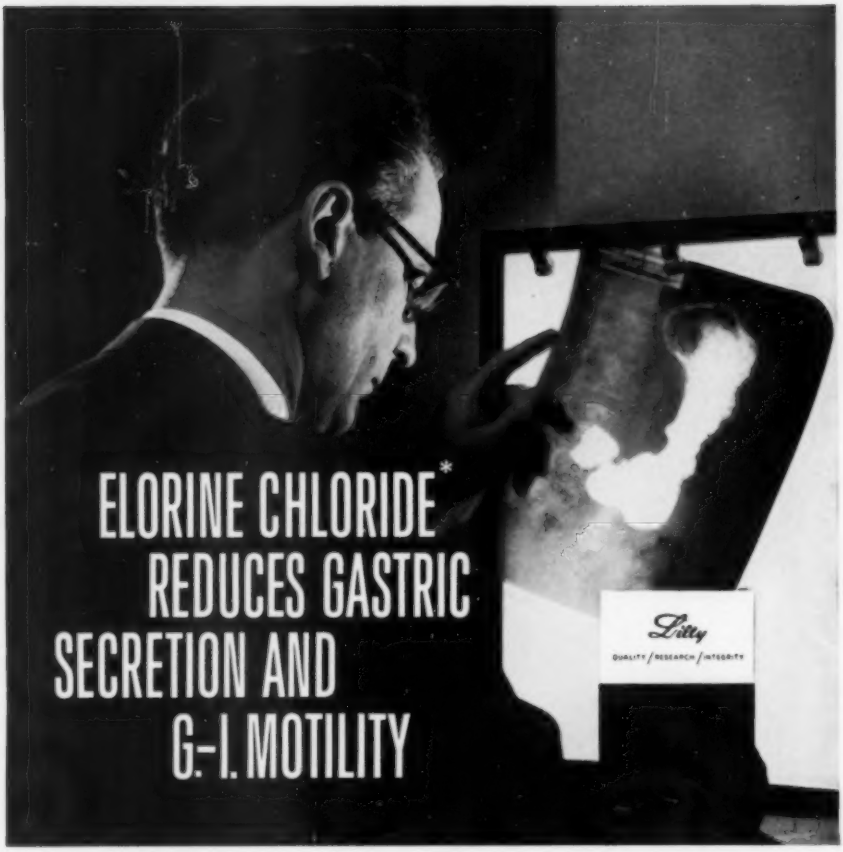

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 34, NO. 10 OCTOBER 1958

THE PATHOLOGICAL EFFECTS OF SMALL DOSES OF RADIATION*

The Fifth Annual Ross Golden Lecture of the New York Roentgen Society

SHIELDS WARREN

Professor, Department of Pathology, Harvard Medical School, Boston, Massachusetts

THE NEW YORK ROENTGEN SOCIETY is most gracious in making me an honorary member and in granting me the distinction of being the first non-radiologist to give this lecture in honor of Dr. Ross Golden, whom I am happy to count among my friends.

Dr. Golden, whose life reaches back into the earlier days of radiology and to whom the radiologists of the present day owe much for his advancement of knowledge and prestige for the profession, was born in 1889, six years before Roentgen discovered x-rays. He, fortunately, is one of the radiologists who has lived beyond the life span of average men and demonstrates that this important profession can be practiced with safety as well as satisfaction.

Radiology early attracted alert and adventurous pioneers who placed the welfare of their patients above their own safety not realizing in the

* Presented at the meeting of the New York Roentgen Society, January 20, 1958, at The New York Academy of Medicine.

early days of the science that safety could be obtained without loss of effectiveness in diagnosis or therapy. Three hundred and two workers in the fields related to medical radiology have lost their lives as a result of the occupational hazards; 197 of these were listed in 1938 on the monument at St. George's Hospital in Hamburg. As medical utilization of ionizing radiation increased, so interest in its biologic effects increased. Pioneer observations demonstrated the effect of radiation in slowing or inhibiting mitosis, producing degenerative changes in cells, both cytoplasm and nucleus, and producing various degrees of injury or necrosis in tissues and organs. The varying sensitivity of the body's cells became apparent within a few years after the discovery of radium and x-rays and by 1910 there was a fairly large, though not generally recognized, pool of knowledge as to radiation effects.

The work of many practitioners and investigators in this country and abroad rapidly advanced the techniques of diagnostic radiology and radiation therapy. Serious attention, however, was not paid for some time to the hazards of radiation, damaged fingers, skin cancer and other disabilities among radiologists, radiologic technicians and radium chemists being regarded as incidental sacrifices to the care of patients. However, the development of better means of detection and measurement of radiation here and abroad, the interest of physicists in radiation and biologic problems led to a clearer understanding and definition of the problems and means of radiation protection. The pioneer work of Failla, Duane, Sievert, Lacassagne, Rock Carling, Regaud, to mention only a few of many, began to call the attention of radiologists and manufacturers of radiation equipment to the need for protection. In the United Kingdom, the first radiation protection committee was established in 1921. The need for their work was further demonstrated by the tragic and vivid experience of the radium dial painters studied so effectively by one of your colleagues, Dr. Martland. A gradually increasing awareness developed throughout the profession that ionizing radiation, although dangerous, could be handled safely. In 1931 a committee established largely through the initiative of the radiologic societies formulated the first code for radiation protection and established a maximum permissible dose of 60 r per year. This followed by almost 30 years the advice of Rollins, one of the pioneers in this country, that the dose should be kept to a dose now thought to be equivalent to 10 r per day.

Today, both the National and the International Committee on Radiation Protection have reduced the permissible dose level to 5 r per year, largely based on the much higher proportion of the population that has entered the atomic energy field. The total number of individuals potentially exposed to radiation is now so large that the older permissible levels might well have added too great a genetic load to our racial pool of mutation. In practice today, as Braestrup's recent study has shown, the actual level of exposure may be as little as 1 r per year. Braestrup believes that radiologists in practice in the early days may have received as much as 100 r per year. Levels acceptable from the standpoint of genetic risk are eminently acceptable from the standpoint of the somatic risks.

While radiologists in recent years have devoted great efforts to preserving the life and health of their patients, there had not been as much attention paid to the protection of themselves and the protection, from the genetic standpoint, of the gonads of their patients.

The widespread public concern with radioactive fallout from atomic weapons tests and potentially from atomic industrial installations led to the formation of the groups both here and in the United Kingdom which issued the National Academy of Sciences reports and the British Medical Research Council report on radiation hazards and also led to the establishment of the United Nations Scientific Committee on the Effects of Atomic Radiation whose report will be published during June this year.

The concern of these groups in determining the sources of genetic exposure to radiation particularly led to the conclusion that aside from natural background in both this country and the United Kingdom incidental exposure of gonads in the course of diagnostic radiologic procedures was the greatest single hazard. Radioactive fallout thus far has contributed only 1 or 2 per cent additional to the natural background radiation. The radiologic societies have taken a very active part in reducing gonadal exposure and this society in particular has been most alert and is helping the New York Academy of Sciences Committees on Radiation Effects to evaluate the practicality of individual exposure records.

It is worth remembering that radiology has moved very rapidly in recent years. It is an index of the rapid progress being made in radiography that the roentgen as a standard unit of measurement was

accepted just over a quarter of a century ago. Information as to the biologic effects of an injurious nature caused by both acute and chronic radiation has been well pointed out in the classic articles of Cantril and Sir Stanford Cade. Some of you may recall the November issue of CA with its vivid picture of the hands of Dr. George Pfahler and one of his young radiologic patients.

The pathologic effects of all types of ionizing radiation are essentially the same, variations in those effects being caused by the amount of energy, time of delivery and degree of penetration of the radiation. In the case of unfiltered radium the effect is in close proximity to the radium, as a cutaneous burn if applied externally or necrosis, necrobiosis or neoplasia wherever it may be deposited in the tissues, as demonstrated so brilliantly by Martland. In the case of soft x-rays the more superficial tissues irradiated show radiation damage. In the case of penetrating x-rays, such as those of one to two-million volts, and the energy from linear accelerators and atomic reactors, the skin is no longer the tissue most susceptible to damage but the more radiosensitive tissues anywhere in the field of radiation are predominantly affected. When poorly penetrating and localized radiation is given in small and repeated doses, it tends to produce skin cancer or more rarely sarcoma of the underlying cutis; if the radiation penetrates beneath the skin and reaches large portions or all of the body, the effect may be manifest through the induction of leukemia or shortening of life span. Leukemia has been demonstrated by March, Ulrich and others to be more prevalent in radiologists than in other practitioners of medicine and than the general population. The studies of the survivors of the atomic bombing of Hiroshima and Nagasaki indicate three important effects: 1) that a single dose of radiation may be effective in producing leukemia; 2) that initially at least only a small part of the heavily exposed population (less than 2 per cent) develops leukemia; and 3) that there appears to be a wave of increased incidence of leukemia between 5 and 10 years after a single relatively heavy whole body exposure. Radiation induced leukemia appears to be of any type and its frequency distribution tends to follow that seen in the general population. Faber has just reported on an interesting study on the incidence of leukemia in Denmark following therapeutic and diagnostic radiation. Eighteen per cent of the patients with chronic lymphatic leukemia gave a history of previous radiation as did 30 per cent of chronic myeloid leukemia patients.

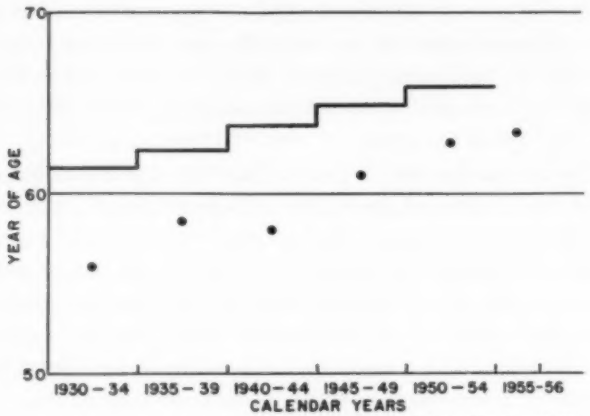
Thirty-two per cent of the cases of acute leukemia had had previous irradiation. This study further showed that particularly in the case of myeloid and acute leukemias such as radiologic diagnostic procedures as had been carried out centered on the thoracic cavity and the abdomen. Faber's study was limited to leukemias occurring in those patients who died over the age of 40 years.

There is statistical evidence from all over the world that leukemia appears to be increasing, perhaps because of better diagnosis, in part because of increased exposure to toxic leukemogenic substances of various sorts, such as benzol, perhaps due to increased use of radiation. Court Brown demonstrated that the x-ray treatment of ankylosing spondylitis led to an increase in leukemia in the patients treated, roughly proportional to dose. Some have even made the unwarranted assumption that leukemia is due to a somatic mutation and that the induction of leukemia is linear in relation to dose. Others, including myself, believe that there is a threshold for the induction of leukemia, and I might even speculate that that threshold for adults lies between 50 and 100 r. The increased incidence of leukemia in children who had been irradiated *in utero* in the course of x-ray pelvimetry of their mothers indicates that the threshold may be lower in infants than in adults. This would be in accord with other observations on radiation effects and indeed some pharmacologic effects.

One of the handicaps in resolving this problem of threshold as against linearity of response with dose hinges on the fact that at low dose levels there may be greater biologic variation in the responses of either humans or test animals than can be detected in experiments. Our currently available evidence in man indicates that the total dose required for the induction of leukemia is large, probably on the order of several hundred rem.* However, even heavy doses approaching the lethal range fail to produce leukemia in many persons.

The stimulus to the study of the chronic effects of radiation provided by the advent of atomic energy and the much wider availability of radioactive substances has led to a number of animal experiments on the effect of varying dose levels on mortality and life span. Many investigators, notably Blair and his associates, have demonstrated life shortening in animals induced by exposure to ionizing radiation. Hardin

* Derived from the initials of *roentgen equivalent man* which, as defined by the International Committee for Radiologic Units, means the dose of ionizing radiation delivered to man and corrected by the relative biologic efficiency factor for the particular type of radiation that happens to be used.



(From Warren, *Klinische Wochenschrift*)

Figure 1.

Jones has marshalled the evidence applicable to man, and suggests that, dealing with the whole population, 1 r of total body radiation substracts 15 days from life span. He points out, however, that other risks than radiation are prevalent. Failla has estimated from experimental and clinical data that the life shortening may be 1.1 day per r. When we think of the many venerable members of the profession of radiology, it seems difficult to accept the idea of life shortening among the members of this profession. However, the experimental evidence is very strong, and I wish to present to you a refinement of the earlier data that I have obtained from the obituary columns in the Journal of The American Medical Association. Figure 1 shows in heavy lines the average age of the male population of the United States over 25 years of age, grouped by calendar quinquennia. This is represented by the heavy lines and shows a steady improvement over the years. I chose over 25 years of age for comparison because few below that age practice radiology. The average age at death of radiologists as taken from the columns of the Journal of The American Medical Association is presented in the form of dots and illustrates that radiologists as a group die five years earlier than the corresponding male population over 25 years of age, but that improvement in longevity of radiologists is demonstrated. This improvement has been particularly marked since

World War II when, thanks to the atomic age, concepts of radiation protection were both more sharply defined and more widely diffused through the population. This life shortening is not due to specific occupational diseases, such as leukemia or skin cancer, but rather to a non-specific effect that might be characterized as premature aging. Thus, whether the cause of death is coronary occlusion, cancer, bronchopneumonia or nephritis, the radiologist on the average is younger than his counterparts among his non-radiologic colleagues or the adult male population. This non-specific effect may be related to almost imperceptible changes in fibrous and elastic tissue and to impairment of mechanisms of immunity. Still further work needs to be done to insure such sound protection or counteraction of effects that the radiologist is not only safe from local injury, skin cancer or leukemia, but safe from subtle generalized injury as well.

I mentioned early in the course of this address that genetic factors were of importance in determining the levels of radiation protection. What data have we on the effects of radiation, either acute or chronic, on the children of irradiated parents to compare with the rather abundant but as yet inadequate mass of information on animals? Because of the clear understanding of its genetic characteristics, the short time period of its generations and the large size of its chromosomes, the fruit fly has been a favorite tool of geneticists. Less work has been done with the mammal. However, the work of Russell on mice indicates that this warm-blooded mammal is, if anything, more sensitive from the genetic standpoint to ionizing radiation than is the fruit fly. Studies on the heredity of man are difficult because of the long span of his generations and because of the complexity of his hereditary patterns. In general, we can assume that a significant proportion, probably less than half, of the mutations carried by man at the present time are due to the background radiation that his germ plasm has received through the course of his development.

The number of genes in man is probably somewhere between 200,000 and 800,000, although this rests on a none too strong foundation. It is clear that radiation induces mutation and that the effect is both cumulative and linear. There exist three studies in man which I believe to have significant bearing on this important point. The survivors of a single dose of acute radiation ranging from just sublethal to just above background have been studied carefully in Hiroshima and Nagasaki

by Neel and Schull. They have demonstrated that in the first generation, where one or both parents had been exposed to radiation from the atomic bomb explosion, there was no significant increase in mutations over the control population. However, the figures are insufficient in number to prove there was no effect. The likelihood is strong that a slight effect did exist.

Macht and Lawrence in 1955 made a questionnaire study based on 2236 radiologists with children. There was an average of 2.69 children per radiologist, a total of 6007. Six per cent of the children with radiation-exposed fathers showed hereditary defects, whereas 4.8 per cent of the children with unexposed fathers had defects. This difference is too narrow to accept as being significant.

Crow, the same year, compared fetal and infant death rates in the progeny of radiologists and pathologists. The wives of radiologists had 16.6 per cent stillbirths and miscarriages. The wives of pathologists had 15.9 per cent, no significant difference. The infant mortality rates in the two groups were also not different but the numbers were very small. On the basis of available studies, therefore, we can assume that there is probably not a significant difference in the incidence of first generation effects in the progeny of radiologists and non-radiologists. However, extensive second generation studies will be necessary before we can assume that man is an exception to the rule and does not show evidence of genetic damage following absorption of radiation by the gonads.

In summary, we may say that cancer of superficial tissues is no longer a hazard to the radiologist; that leukemia apparently is a hazard but may be minimized by adherence to the present standards of protection; that shortening of life span is a hazard, but that this is rapidly being eliminated by current standards of protection; that we may expect man, including radiologists, to follow the same laws of transmission of hereditary characteristics as other mammals; and that the present rules for protection reduce the exposure risks to acceptable levels.

THE ANATOMICAL AND PHYSIOLOGICAL ASPECTS OF CORNEAL SURGERY*

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THE healing of corneal wounds presents special features which are dictated by the structure and chemical constitution of the cornea, and the physical conditions under which it takes place. Corneal wound healing will be discussed in relation to the ultramicroscopic structure of the fibers, the metabolism of ground substance components, the tension on the wound induced by intraocular pressure, activation of corneal cells in early stages of healing, and the structural basis of transparency. The cornea consists of very regularly arranged collagen fibrils, which are grouped in lamellae. Between the fibrils and the lamellae is the ground substance of connective tissues; the vehicle through which the metabolites are conveyed, and the component which is subject to the greatest variation in volume by the loss or gain of fluid. Within the ground substance and between the fibers are the cells of the corneal stroma, the keratocytes or fibrocytes. These are responsible for the synthesis and maintenance of both the fibers and ground substance. All three components of the cornea, cells, ground substance and fibers, are involved in healing.

We all have a clear idea of the function of fibers and cells, but that of the ground substance is not well known. Ground substance is present in all connective tissues. It is related anatomically to the fibers, but by an unknown means. During the past 20 years the chemistry of connective tissue ground substance has made great strides, primarily through the research of Karl Meyer and his associates[1], who have demonstrated the presence of three acid mucopolysaccharides (keratosulfate, chondroitin sulfate A, and chondroitin), as major constituents

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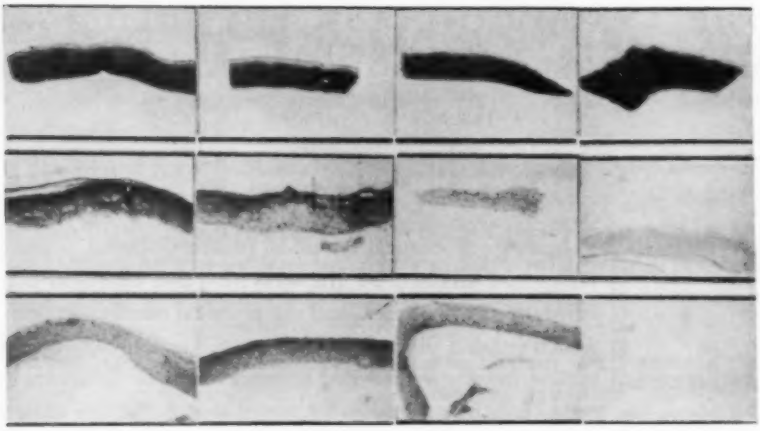

Figure 1.—Radioautographs of cornea (above) sclera (middle row) and pulmonary artery (lower row). The density of the autograph indicates the amount of S^{35} incorporated in the tissue at the time of autopsy. The S^{35}, injected intravenously as Na_2SO_4, was administered 1, 6, 12 and 24 days prior to autopsy. The cornea, sclera and artery shown in each verticle row were from the same animal and the amount of physical decay of the S^{35} was identical in all tissues shown. The figure demonstrates that the biological turn-over rate of sulfate in the cornea is far slower than in the sclera or artery.

in the cornea. Because the chemistry of these compounds has been well studied, their metabolism is beginning to be understood. They are far from inert, but are rather in a state of constant "turn-over". For example, 50 per cent of the hyaluronic acid in rabbit skin is destroyed and re-formed every 3.7 days. The sulfated mucopolysaccharides of skin have a longer half-life—50 per cent being "turned-over" every 7.7 days[2]. The cornea contains an apparently unique keratosulfate in addition to chondroitin sulfate A and chondroitin, and the "turn-over" time of the sulfated corneal mucopolysaccharides is much longer than the equivalent periods for other tissues. Apparently, 50 per cent of the sulfated materials in the cornea are replaced once in approximately 32 days[3]. This figure may be exaggerated due to the possibility that freed sulfate radicals may not diffuse out of the cornea before they are re-synthesized into a new molecule of some sulfated mucopolysaccharides, thus introducing an error in the calculation of the turn-over rate. The marked difference in the turn-over rate of sulfated mucopolysac-

charides of the cornea and other connective tissues (sclera and a large artery) is demonstrated in Figure 1. Radioautographs were prepared[4] of the cornea, sclera and an artery of rabbits which had received isotopically labelled sodium sulfate one, six, 12 and 24 days prior to autopsy. All three tissues incorporated considerable amounts of radioactive sulfate, but in the cases of sclera and artery the sulfated material was rapidly replaced so that by 24 days almost all of the sulfate contained in them had been supplanted by new non-radioactive material. The cornea, however, retained a large proportion of the radioactive sulfate even after 24 days.

The slow turn-over rate of a fundamental corneal constituent allows an old problem to be attacked: the question of replacement of corneal grafts. We still do not know if a corneal graft retains its donor identity or is slowly replaced by the host. This question which was so real when propounded originally, has lost much of its significance, for today we do not regard any tissue as absolutely static and unchanging. The normal cornea is always being renewed, although at a slow rate. Dohlman[3] has labelled donor corneas with radioactive sulfate which was incorporated as a part of the corneal ground substance. Such corneas were used as transplant donors. He was able to show that except for an initial partial replacement of the sulfated compounds in the graft, the bulk of the original sulfated mucopolysaccharide of the transplant remained, indicating that this component of the original donor tissue persists in the transplant.

These constituents of the ground substance are relatively easily removed from the fibers without recourse to drastic chemical treatment, since the forces linking collagen fibers and acid mucopolysaccharides are weak. Mucopolysaccharides are clearly related to fiber formation, both in embryonic development of the cornea[5] and in the healing of its wounds[6], but the significance of this relationship has not yet been elucidated. They increase in amount when fibers form, and have been implicated as a necessary factor in the production of collagen fibers *in vitro*, but there is, as yet, no conclusive evidence that the presence of these materials is necessary for fibrillogenesis *in vivo*.

The quantity and location of the sulfated mucopolysaccharides, keratosulfate, and chondroitin sulfate, can be determined in tissues by radioautographic techniques. Sulfated materials appear very early in a healing wound, and their rate of synthesis is and remains high for a

long time in the area of the regenerating connective tissue[6]. While the healing process involves the formation of sulfated mucopolysaccharides, the preceding injury, i.e., the surgical incision, causes some reduction in the ground substance in the adjacent tissue. For this reason, at the initiation of the healing process there is probably a deficit in ground substance materials in the cornea surrounding the wound. This can be seen by examining sections of an early corneal wound stained with toluidine blue. The ground substance constituents stain metachromatically with this dye and one can see that metachromasia is reduced in the tissue near a cut. Of course, this area is also subject to swelling which of itself would weaken the intensity of the staining reaction. However, the change appears to be of a magnitude too great to be explained by swelling alone, thus indicating a reduction in the absolute amount of ground substance.

Healing is a function of the cells, both of the epithelium and of the connective tissue. The epithelium promptly covers the defect caused by the incision, following which the swelling attendant to the break in the epithelial barriers is reduced. The tendency and capacity of the cornea to swell in physiological media is far greater than that of other connective tissues. This tendency is combated throughout life by the epithelia on both surfaces, which remove water from the corneal stroma by a means still controversial. This activity is an aerobic one, requiring oxygen for its work. Because the cornea is avascular, dense and far removed from a blood supply, it is partially dependent on atmospheric oxygen[7] for its normal function. Even in the normal cornea the sources of oxygen available to it are not adequate for maximum efficiency[8]. The epithelium no doubt plays a role in the healing of connective tissue wounds other than restoring and maintaining the fluid balance of the cornea, for the first connective tissue fibers which form in a wound are found adjacent to the epithelial cells[6]. In vascular connective tissues the first signs of healing are near the capillaries, which supply that tissue with its oxygen and sources of energy. In the avascular cornea the anterior surface is the richest source of oxygen and due to the glycogen content of the epithelium, of nutrition also.

It is difficult to establish which connective tissue cell elaborates the ground substance and as a result more than one cell type has been implicated. The experiments of Grossfeld, Meyer, Godman and Linker[9], however, clearly indicate that the fibroblast is the source of at least

some ground substance constituents. They were able to demonstrate that cultures of fibroblasts produced hyaluronic acid and a chondroitin sulfate.

The keratocytes are, as expected, important agents in the synthesis of new fibers, but in the normal cornea they are not active in this respect, for in normal tissue collagen fibrils are replaced at an extremely slow rate. Connective tissue cells when spinning out new fibrils are quite different, structurally and functionally from the quiescent fibrocytes, and are, therefore, called fibroblasts. For many years it has been accepted that the fibroblasts produce the collagen fibrils and many speculations on this process have been made. Some have suggested that the collagen fibrils are precipitated in the fluid or ground substance near the fibroblasts, whereas others have insisted that they were synthesized intracellularly and subsequently extruded. Neither appears to be the case. Investigations with the aid of the electron microscope have clarified this problem. The first immature fibrils appear on the surface of the fibroblasts[10]. At this stage they are without the characteristic collagen periodicity of 640 Å. Their relationship to the cell membrane is so intimate that it appears as if the fibrils were in fact a part of this membrane and were peeled off in long strands. There can be no doubt from these studies that the process of fibrillogenesis is neither intra- nor extracellular, but is one of the cell surface.

What mechanisms cause the conversion of an apparently static keratocyte to one of this type? This question cannot now be answered, but if the activation is analogous to that which mobilizes leukocytes at a wound, the primary stimulus is the wound itself. Reports by Weimar[11] show that the tissue injury attendant on the cleanest surgical incision releases in the tissue fluid proteolytic enzymes, which split the tissue proteins into peptide units, the definitive mobilizing agents. Such a mechanism produces the invasion of a wounded cornea by polymorphonuclear leukocytes and of monocytes from the blood stream. During metamorphosis of a keratocyte into a fibroblast, the nucleus and the cytoplasm increase in size and in the amount of cytoplasmic and nuclear ribonucleic acid. The presence of this material is necessary, perhaps as a template, to guarantee the orderly assembly of amino acids, and indicates production of protein. Not only are the fibrocytes near a cut mobilized in this fashion, but the monocytes, which quickly reach the wound area from the limbal vessels, also metamorphose into fibro-

blasts. In fact, monocytes contribute two or three times more fibroblasts to a healing wound than do the original corneal corpuscles[12].

It is obvious that the corneal lamellae and gross fibers are nearly parallel and are regularly arranged. This regularity extends to the sub-microscopic level as shown by the fine work of Jakus[13], and is of fundamental importance, as will be discussed later, to transparency of the cornea. The sub-microscopic structure of healing cuts of the cornea has not yet been investigated, but studies have been made on another tissue, the basement membrane of amphibian skin. This structure has an extraordinary resemblance to the cornea in the arrangement of its fibrils. Paul Weiss[14] has shown that the first fibers which are formed in a healing wound are distributed in an heterogeneous fashion. Organization is imposed upon them after the initial closure of the wound. One does not know if or how this takes place in the cornea, but from light microscope studies it appears that the process is essentially the same. The first fibers which may be seen in a healing cut are reticular, and arranged in a completely heterogeneous fashion. The fibers in a similar wound 45 days later are far more regularly arranged simulating the condition in the intact cornea[6]. What mechanism causes this arrangement? It would appear that stress or tension plays a large part in this. Tendons also are made of collagen fibrils which are rather regularly arranged. If a wound is made in a tendon which has been severed from its muscle, thus removing the normal tension on the fibers, healing is accomplished by regenerated collagen fibrils disposed in a completely irregular fashion. If regeneration occurs while the tendon is under its normal stress, the fibroblasts and the fibrils which they produce are arranged parallel to the lines of tension[15]. The first hours of fibrillogenesis in a corneal wound are concerned with the uniting of the cut edges. During this period the stresses in such an area would be complicated. One may postulate that with the re-establishment of normal intraocular pressure and the resultant corneal tension, new fibers would be oriented in a parallel manner, as in the tendon.

Apparently this arrangement is important, for it deals with the transparency of the cornea. It is not enough that a corneal injury be repaired and the globe made intact. It is also desirable that the regenerated and adjacent tissue be transparent. There are many theories offered to explain the transparency of the cornea. The most recent and fruitful one was propounded by Maurice[16], a "lattice" theory which

points out that in the cornea the small diameter, the regularity of the size and arrangement of the ultramicroscopic fibrils are the essential features which make this tissue transparent. The spaced fibrils behave as an infinite number of diffraction gratings. Because of their number and regularity of their arrangement, the intensity of the maxima is reinforced by the diffracted light and relatively little is lost by scatter. The fibrils of the cornea have been shown to be very thin as compared to those which make up the sclera or even a corneal leukoma. The diameters of the corneal fibers are not very variable, whereas those of the opaque sclera or of a leukoma are so, demonstrated by the study of Schwarz[17]. According to Maurice, for a tissue to be transparent, it is necessary that its fibrils be parallel, equal in diameter, and have their axes disposed in a lattice. We know that the corneal fibrils are fine, parallel and equal in diameter. The x-ray defraction patterns of the cornea presented by Maurice are evidence that the fibrils are disposed in a lattice, thus permitting transparency. It is also suggested that one function of the interstitial mucoid may be in maintaining the orderliness of their arrangement. When this orderliness is disturbed by swelling of the ground substance, changes in the spatial arrangement of the fibrils occur with resultant clouding. This theory gives us a framework in which the mucoid and the regularity of the corneal structure can be related to its transparency.

Summary

After an incision has been made, the inevitable tissue damage releases proteolytic enzymes. The product of their action may be the agent which mobilizes the heretofore inactive keratocytes and attracts the monocytes of the blood to the site of injury. There they and the fibrocytes metamorphose into fibroblasts within the first 36-48 hours. One of the first activities of these cells is the synthesis of acid mucopolysaccharides. Essentially concomitant with this process is the formation of the first fine reticular fibrils. These are irregularly arranged, but the fibers formed later, as the wound is strengthened, are parallel to the surface of the cornea. This is accomplished over a long period of time, during which the ground substance is synthesized at a much higher rate than in the normal cornea. The process of rearrangement of the fibrils to form nearly parallel lamellae is not known. Possibly the first fibrils may be regarded as emergency scaffold-

ing and are re-absorbed bit by bit as the definitive fibers are formed. If so, the collagen and probably the ground substance also would possess a much higher "turn-over" rate than in the normal cornea. If this picture is correct, a healing wound is the site of extreme activity for a long period, during which synthesis and destruction of components are followed by their re-synthesis as the corneal structure is re-formed.

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THERAPY OF COMMON ENDOCRINE DISORDERS

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR JOSEPH W. JAILER: In opening this panel discussion on "The Therapy of the More Common Endocrine Disorders" I should like to emphasize the fact that for the rational and effective use of the powerful therapeutic agents which are now available we must have accurate diagnosis. Diagnosis in the field of endocrinology, as in other fields of medicine, is based on a careful history and physical examination, with confirmation at the laboratory level. Too often have we been asked to explain why a certain hormonal preparation is ineffective, only to find that the diagnosis was wrong in the first place. For example, the administration of as much as 10 grains a day of thyroid may cause no weight reduction or increase "energy" in an individual because that patient did not have hypothyroidism originally. We have available some very specific and precise laboratory tests, and they should be used in all cases to confirm the suspected diagnosis. With this in mind our discussion will be confined to the treatment of the various endocrinopathies, assuming accurate diagnoses.

In addition to Dr. Henry Aranow, Jr., and Dr. Melvin M. Grumbach who are present today, the panel was to have included Dr. Charles Lee Buxton, Professor of Obstetrics and Gynecology at Yale University School of Medicine. Unfortunately, Dr. Buxton has been unavoidably detained in New Haven by the exigencies of obstetric practice. Because of my close association with Dr. Buxton over the years I think I can summarize in a few sentences some of his feelings on the matter of the endocrine treatment of some gynecological disorders, but I, not Dr. Buxton, will assume responsibility for the conclusions presented. However, let us start with Dr. Grumbach, who will discuss some of the more common endocrine disorders seen in childhood.

DR. MELVIN M. GRUMBACH: The first topic for discussion this afternoon is the management of cryptorchism. This is a most controversial subject, and some of our most distinguished colleagues in surgery and urology differ radically in their views as to when surgery should be performed. I suspect Dr. Jailer asked me to discuss this in order to promote a lively discussion period, but perhaps also because we are basically conservative in our use of endocrine therapy. Something might also be said for a detached and, therefore, hopefully unprejudiced presentation of the evidence. As you will see, there is a serious lack of knowledge in this field on which to base firm conclusions. The descent of the fetal testes from an intra-abdominal position into the scrotum

occurs at about the eighth month of gestation. It is of interest that the testes are located in the scrotum from infancy through adulthood only in man and some of the other primates. Some cases of maldescent are due to ectopic position, but in the majority of instances arrest occurs along the normal pathway of migration.

What is the incidence of cryptorchism? A recent careful study by Scorer in England indicated that 3.4 per cent of full term male infants were found to have incompletely descended testes. During the first month descent occurred in 50 per cent so that at one month of age the incidence of incompletely descended testes in this large series was 1.7 per cent. This figure should be compared with an estimated incidence of 0.1-0.3 per cent in adult males. The difference in incidence is a reasonable albeit crude approximation of the role of spontaneous descent. The observations of Johnson in over 500 boys with undescended testes suggest that in the majority of cases this descent occurs before 15 years of age.

In our thinking about cryptorchism we must clearly distinguish true undescended testes from retractile testes. In the latter the testis is pulled into the inguinal canal and sometimes into the abdomen by contraction of the cremasteric muscle. This differentiation is not always easy and even experienced examiners have, on occasion, been misled. I believe the failure to recognize physiologic retraction of the testis has led to some of the difficulties in interpreting the results of treatment. Obviously, treatment of a retractile testis will produce good results.

For every boy with true undescended testis we see three to four children referred for cryptorchism who are found to have a retractile testis on examination. The distinction may only be possible after several examinations, and it is especially difficult in obese boys. Careful and deliberate examination in an erect and supine position, examination of the patient in a sitting position, while he performs the Valsalva maneuver or examination after a warm bath or the application of warm packs, usually will settle the question. Failure to detect a testis should be confirmed by subsequent examinations at later visits.

In rare instances some individuals with maldescent of one or both testes, especially when this condition is associated with hypospadias, exhibit ambisexual development of the reproductive structures. Cryptorchism is a cardinal sign of hermaphrodism, and this possibility should be kept in mind. Turning to the management of the cryptorchism, the

primary question hinges not on whether orchiopexy should be performed but rather at what age surgery should be resorted to.

Let us examine the reasons proposed for performing orchiopexy and their validity in regard to the age at which it should be performed. First, an undescended testis is commonly associated with an inguinal hernia. When a hernia is clinically evident, there is universal agreement that orchiopexy should be performed at the same time that the hernia is repaired. Trauma and torsion—the abdominal testis is more prone to torsion and the inguinal testis is more prone to trauma—are relatively uncommon complications of cryptorchism.

Another indication for early orchiopexy that has been proposed is the possibility of neoplastic change. An accurate estimate of the incidence of neoplastic degeneration in undescended testis is not available. There is reasonably good evidence, particularly from the data obtained in male pseudohermaphrodites, that the incidence of neoplasm is greater in cryptorchic than in normally descended scrotal testes. The published figures suggest that testicular cancer is 10 to 50 times more common in undescended testes; about 20 times is the majority opinion. These estimates are based on retrospective studies in patients with testicular tumors. They do not give a complete or precise picture. Testicular tumors are rare. In certain varieties of male pseudohermaphrodites, the incidence of tumors in undescended testes is unusually high. Neoplasia is not a problem before early adult life and actually bears more on the question of whether orchiectomy should be performed in cases where intra-abdominal testis cannot be brought into the scrotum. Moreover, there is an increasing amount of evidence which suggests that when neoplastic degeneration—and this applies especially to seminoma—occurs in cryptorchic testes, these testes are inherently defective. Tumors have occurred in these testes following orchiopexy and, in cases of unilateral cryptorchism, in the normally descended scrotal testis. In summary then, the incidence of neoplasia is not great in undescended testes but it is significantly higher than in scrotal testes.

Another reason is the psychologic factor. Reference is frequently made to psychic trauma resulting from the cosmetic defect. We are unimpressed with this consideration in preadolescent boys and indeed there is little evidence to support such a contention. It is true that psychologic difficulties may play a more important role as puberty approaches and in adolescence.

There is no evidence to indicate that the development of secondary sexual characteristics is delayed because of abnormal position of the testes or that hormonal secretion is improved following early repair of the undescended testis.

The main reason advanced in support of orchiopexy is the preservation of fertility. This is the most confused and controversial and also the most important aspect of the problem. There is agreement that if cryptorchism is untreated during or after puberty spermatogenic activity is diminished and in time severe degenerative changes occur, presumably due to thermal injury.

In instances of bilateral cryptorchism this would result in infertility. Careful studies in unilateral cryptorchids comparing the microscopic appearance of a cryptorchic testis with its scrotal mate, have shown that there is a lag in the development of the seminiferous tubules in undescended testes as early as five to six years of age. However, these are changes of delay in development rather than of degeneration. Evidence is lacking to indicate that they are of a permanent nature before puberty is well advanced. Studies of the microscopic appearance of cryptorchic testes after orchiopexy, even when performed at an early age, generally have shown poor spermatogenesis. These and other changes in the testicular morphology would seem to indicate that many cryptorchic testes are basically defective, a suggestion made by John Hunter more than a century ago. However, the true incidence of congenital defects in these cases is not known. Nor have adequate criteria been established for their consistent detection. Also, the poor results may be due, at least in part, to damage to the testicular blood supply from the orchiopexy procedure. It is estimated that after this procedure, gross atrophy appears in about 10 per cent of the testes, in addition to those testes damaged but which are of normal size. Thus there is a risk of losing the endocrine as well as the spermatogenic function of the testes. Further, in unilateral cryptorchism one would not expect fertility to be impaired should the condition not be corrected provided the opposite testis is normal.

The best data concerning the effects of orchiopexy on fertility are those obtained in cases of bilateral cryptorchism. Most of these studies have shown very disappointing results, with one notable exception. In the study of Gross and Jewett from the Boston Children's Hospital, investigation of 38 patients in whom orchiopexy had been performed

before 11 years of age, in most cases between 9 and 11 years of age, revealed that 79 per cent were fertile or potentially fertile 7 to 30 years after the procedure. The unanswered question remains: "What is the probability that a preadolescent boy with bilateral undescended testes, if left untreated until the onset of puberty, will reach adulthood with fertile scrotal testes?"

The plan of management to be recommended attempts to take into consideration, in the light of present knowledge, the possibility of spontaneous descent, the potential for fertility, and the possibility of trauma to the testes from orchiopexy.

We do not know the optimum age for treatment. Hormonal therapy and surgery both have their exponents but there is much difference of opinion as to the role of either in both unilateral and bilateral cryptorchism. In some cases the testes are inherently defective and neither form of treatment can meet with success. Usually, we recommend orchiopexy between 9 and 12 years of age. In any case, signs of early puberty, such as development of pubic hair and enlargement of the penis and scrotum are indications for surgery in these patients. Delaying therapy until this age would permit a number of testes to descend spontaneously and thus avoid the danger of testicular injury from orchiopexy at an early age. The testis is also larger and orchiopexy can be accomplished with greater facility than in younger boys. Most surgeons prefer to correct only one undescended testis at a time and to defer repair of the opposite testis for several months.

As for hormonal treatment, the results are disappointing. I believe it has a limited role in unilateral cryptorchism, particularly if descent has not occurred by early puberty. In cases of bilateral cryptorchism it is sometimes indicated if an endocrine disorder is present or as a therapeutic trial before orchiopexy is recommended. In young boys enthusiastic and prolonged therapy often results in precocious sexual development. If hormones are used, the plan of Engle and Robinson, employing 4,000 to 5,000 units of chorionic gonadotropin daily for 3 days and waiting 7 to 10 days before advising surgery, or that of Heller and his associates, using 4,000 to 5,000 units three times a week for a total of 40,000 units are reasonable approaches to the problem. If descent does not occur, orchiopexy is promptly performed. Finally I should like to say a word about the surgical procedure because I believe this is also an important factor. Many surgeons are now abandoning the Keetley-

Torek procedure because of the tension placed on the spermatic vessels and the danger of compromising the blood supply to the testes from this procedure. Gross, among others, believes that this procedure may be the cause of infertility in many instances.

Adequate dissection of the cord, mobilization of the spermatic blood vessels, intra-abdominally if necessary, are important in order to avoid insofar as possible, injury to the testes following this procedure.

I might say in closing that there is insufficient evidence to be dogmatic about any plan of management. On the basis of the evidence at hand, we believe this plan of management is justified. I think you will agree that there is a great need for controlled studies of the course and the effect of treatment of this common pediatric disorder documented by testicular biopsy and by the incidence of fertility or potential fertility in adulthood.

MODERATOR JAILER: Thank you, Dr. Grumbach! I am sure that we will return to this subject in the discussion period. I have asked Dr. Aranow to discuss the treatment of hyperthyroidism and hypothyroidism. After he has finished, I should like to have Dr. Grumbach discuss the thyroid from the viewpoint of the pediatrician.

DR. HENRY ARANOW, JR.: In discussing hyperthyroidism it is clinically important to distinguish between that type of hyperthyroidism which is due to diffuse toxic goiter, otherwise known as Graves' disease, and the type produced by hyperfunctioning adenoma, which has been called Plummer's disease. In the latter condition we do not see the eye complications and the response to the antithyroid drugs is quite different from that of the diffuse toxic gland.

We have available to us in the treatment of hyperthyroidism a variety of agents, all of them reasonably effective and our choice is one between riches, rather than, as is so often the case, a choice between evils. We can influence the thyroid function with iodine and with the antithyroid drugs. We can destroy the thyroid gland with radiation, and we can remove it with surgery. I shall discuss these agents in order.

Iodine is still a very valuable agent and although its *modus operandi* is not thoroughly understood, there is a good deal of evidence which indicates that, in the hyperthyroid individual who has a diffuse toxic goiter, iodine slows the release of the thyroid hormone from the hyperactive gland and decreases the hyperplasia of this gland. The best

hypothesis to account for this is that, in some way, it interferes with the action of thyrotropic hormone. The use of iodine is of great value in the preoperative management of patients with thyrotoxicosis whether or not the antithyroid drugs are given as well. It is also useful in the control of very mildly thyrotoxic individuals and permanent remissions can often be secured in patients with apparently self-limited disease, when the hypermetabolic state is controlled with iodine alone. It should be emphasized, however, that protracted use of iodine, unless euthyroidism is promptly obtained in the patient, is not an effective or an adequate therapy for the hyperthyroid individual.

The antithyroid drugs—and in this discussion I shall limit myself to those which contain the thiourea complex—(the thiocyanate, perchlorate group are of academic interest but I do not think are useful practically)—which act by preventing the new synthesis of thyroid hormone. From the time of their administration, when given in adequate dosage, they almost invariably prevent the new synthesis of thyroid hormone. They do not in any way influence the release of hormone previously stored in the gland so that we must wait for their effect until previous hormone stores are exhausted. If we fill up the gland with new hormone by the prior administration of iodine, we will then have to wait that much longer for our clinical effects, since the body will take that much longer to metabolize the preformed thyroid hormone. The appearance of the effect of the drug is more prompt when the gland is relatively empty of hormone and when its rate of utilization is high, as in the thyrotoxic individual. In almost all cases hormone synthesis blockage can be attained by the use of these drugs, although it is not infrequently necessary to use amounts considerably larger than the conventional doses in some patients and complete suppression of the incorporation of iodine in the thyroid hormone, for example, requires about 40 mg. of Tapazole three times a day, or about 1200 mg. per day of propylthiouracil in divided doses.

All of these drugs possess certain toxic potentialities. They will produce skin reactions and these average somewhat less than 5 per cent with propylthiouracil and about 5 per cent with Tapazole. They produce agranulocytosis in about 0.5 per cent of patients. This means that about one instance of agranulocytosis can be anticipated in every 200 patients treated. There may be drug fevers, as with any drug, and less common reactions such as loss of hair, loss of taste, thrombocyto-

penic purpura, hepatitis, and neuropathy have been described. Anyone prescribing these drugs should be aware that the appearance of one of these symptoms may be the result of drug administration. The antithyroid drugs have two roles in the treatment of thyrotoxicosis. One role is a preoperative one, by reducing the patient's toxicity so that he is euthyroid at the time of operation. The operative procedure is thus made much more safe. The surgeon can operate on a patient who is in much better medical condition, resulting in lower morbidity and mortality rates and a considerably higher cure rate. The other role is in the use of the antithyroid drugs as permanent agents with which to attempt to obtain a permanent remission. It is pretty well conceded, and the evidence supports it, that by the continued administration of these drugs almost all patients with thyrotoxicosis can be kept under control and in the euthyroid state. However, the incidence of toxicity, although it is highest in the early weeks and months of treatment, does not become negligibly small even after months and years of treatment. Any patient taking an antithyroid drug may at any time during the course of his therapy develop one of the toxic reactions that I have listed. When we speak about remissions produced by the use of antithyroid drugs, we are talking about a relatively fixed term of treatment, after which we anticipate withdrawal of the drug and the lack of need for the drug because the patient no longer is hyperthyroid.

The figures for permanent remissions obtained with courses of treatment of 18 months, more or less, vary because the number of patients lost to medical therapy depends upon a host of factors: the attitude of the physician, the availability of good surgeons, the competition from enthusiasts for radioiodine, etc. In clinics in which a firm decision has been made that only the antithyroid drug therapy will be available, until the person in charge decides that there are indications for other modes of therapy which are compelling, remission rates as high as 78 to 89 per cent in diffuse toxic goiters have been obtained. In some of these patients, however, a number of years of treatment have been required.

In the American series where this control has not been effectively imposed, the usual figure and the figure in my own personal series is about 60 per cent.

I believe that when one is initiating therapy, one should get an initial white blood count and differential. Remember that leukopenia

and *relative* granulopenia are common in thyrotoxicosis and if one starts with 42 per cent polys, and a count of 4,000, the appearance of a count with 38 per cent polys and 3800 cells is not an indication for interrupting therapy. I myself do not ask the patient to have repeated routine white blood and differential counts. I thoroughly indoctrinate him or her in the symptoms of agranulocytosis, of drug rash, etc., and ask him or her to call me at once, or to come to the clinic for a white count if any of these symptoms occur. I believe that routine blood counts induce in the patient a false sense of confidence in the physician, because the count may be normal on Thursday and the patient may develop agranulocytosis on Saturday and not report symptoms because he has been reassured on Thursday.

Turning now to radiation, we find it is a means of destroying hyperfunctioning thyroid tissue. It is available to us in two forms: external radiation by means of roentgen rays and internal radiation by means of radioactive iodine. I think it can be fairly said that external radiation has now been largely replaced by radioiodine since the external radiation produces an excessive radiation of the skin and is not very effective in large glands whose deeper surfaces are more or less inaccessible to the radiation.

Radioiodine produces its remission by the production of ionizing radiation and the concentration of this radiation in the thyroid gland. Since it is picked up like inorganic iodine in general, incorporated in the hormone of the gland, moves through the thyroid cells, and is stored in the colloid, it is uniformly effective. There have been no instances in which control of thyrotoxicosis could not be achieved by enough radioiodine. However, the effects of a given dose of radioiodine are not fully evident for a period of about two months and if one wishes to avoid a large incidence of hypothyroidism, one must resign oneself to the need of giving several doses. If one picks out a fixed dose which will give a remission rate of, let us say, 80 or 90 per cent with one dose, one can anticipate an incidence of hypothyroidism, of a more or less permanent nature, of more than 30 per cent.

In our clinic we prefer to give relatively small doses with the idea that it may be necessary to repeat the dose, if at the end of two months it turns out to be ineffective or inadequate. Unfortunately the biologic variation is the controlling one, and the number of roentgen equivalents physical per gram of thyroid required by one patient to produce a

remission may be two to three times as great as that required by another. Occasionally, in extremely toxic patients, the administration of radioiodine may cause an exacerbation of the thyrotoxicosis which may produce a storm in an extremely toxic patient. The drug must be administered with care and when radioiodine is indicated, the group at the Lahey Clinic actually prefers to reduce the thyrotoxicosis with antithyroid drugs, to interrupt antithyroid therapy and give the radioiodine therapy and then to reinstitute antithyroid drug therapy. Radioiodine does not produce hypoparathyroidism, nor laryngeal nerve palsy nor airway obstruction. The disadvantages are largely potential. In addition to the one I mentioned in the very toxic individual, there is unequivocal evidence that ionizing radiation may be carcinogenic. We do not know whether or not this will be true of the doses used in the treatment of hyperthyroidism. We know, indeed, that the doses used in the treatment of thyroid neoplasm may produce leukemia in a significant number of patients. We have, therefore, in our clinic, and in most of the clinics of the country, reserved the use of this agent for people in an older age group, the idea being that it will take a couple of decades for the carcinogenic activity of the compound to manifest itself, and by that time the patients will be relatively well along in years. The disease which would be produced is one of relatively slow progression so it is felt that radioiodine can be employed in these patients with relative safety even though it may ultimately prove to be carcinogenic.

The use of these ionizing radiations in the young may be employed if the potential carcinogenic risk seems to be significantly less than the risk of other modes of therapy. In patients with recurrent thyrotoxicosis after surgery, permanent remissions with antithyroid drugs are rather infrequent and a second operation for thyrotoxicosis involves a much greater hazard from recurrent laryngeal nerve injury and from hypoparathyroidism than does the initial operation. It is our practice to use radioiodine in the therapy of recurrent toxic goiter.

Finally, a word about surgery: it should be realized that I speak as an internist. Surgery is reported to be an extremely effective mode of therapy with a very low incidence of untoward side effects. These reports are true but the surgery discussed in these reports is done by trained thyroid surgeons who do a great deal of this type of surgery. Crile estimated as recently as a decade ago that the over-all mortality throughout the country from the surgical treatment of thyrotoxicosis

by all types of surgeons was about 10 per cent, which is a staggering figure.

A few years ago the group at the University of California Clinic reported its mortality rate as 1 per cent; this is a thyroid clinic through which residents in training rotate under the guidance of trained thyroid surgeons. Their vocal cord paralysis rate was 2.7 per cent. Their vocal cord paresis rate was 3.3 per cent. They had hypothyroidism in almost 30 per cent, with frank myxedema in 9 and a recurrence rate of 3.2 per cent. This low recurrence rate probably explains in part their high hypothyroid incidence.

This summarizes 12.5 years of treatment in this clinic and although it is a treatment which is obviously effective it has certain risks.

Having briefly outlined these various methods of treatment I should like to ask, "How does one choose between them?" or let us say "How do I select which of these modes of therapy to employ?" Before answering that, I should mention ophthalmopathy as one of the major and most threatening complications of hyperthyroidism as we see it in Graves' disease. When we see a patient whose eyes indicate serious involvement of the orbital structures in a process not understood, which we call infiltrative ophthalmopathy we are alarmed by the picture and proceed with great caution.

It appears to us that any measure which rapidly reduces the metabolic rate has hazards, so that, in our opinion, surgery should not be employed in patients whose eyes are threatened. It appears equally safe to use small and repeated doses of radioiodine or the antithyroid drugs, provided these are used with caution. Since one can reverse one's field rather readily with the antithyroid drugs, I personally favor them as the agents of choice in the management of those patients whose eyes are threatened with irremediable damage. This includes those patients who have chemosis, actual proptosis or involvement of the extraocular muscles. It should be emphasized that the ophthalmopathies bear no relationship to toxicosis and the presence of very severe eye signs may be noted in conjunction with very slight increases in metabolic rate. One should proceed cautiously before administering any agent which will further reduce the metabolic rate in a patient with eye signs who has had previous thyroid surgery. In this group of patients I prefer first, the antithyroid drugs and second, radioiodine.

In children—and Dr. Grumbach will comment further on this later—

the results of surgical therapy have not been as good as they have been in adults. On theoretical grounds the hazards of radiation seem much greater and it has been my policy to follow these patients on courses of antithyroid therapy, prolonged if necessary.

In a series in which Dr. Grumbach participated, the remission rate was pretty close to 70 odd per cent in children under treatment. In young adults with large glands the permanent control of thyrotoxicosis with antithyroid drugs is not readily achieved. In general most of those patients do well when their thyrotoxicosis is brought under control with antithyroid drugs, iodine administered to reduce the vascularity, and surgery performed. However, a few of these patients with relatively small glands will be controlled with rapidly diminishing doses of antithyroid drugs and many of them deserve a trial on these drugs to determine whether or not a spontaneous and permanent remission can be effected on these drugs alone.

Finally, in our clinic patients 45 years old and older, with diffuse toxic goiter, are treated with radioactive iodine and the results, as I have already indicated, are excellent.

A word about hypothyroidism. Hypothyroidism pre-supposes a high index of diagnostic suspicion on the physician's part and the establishment of the fact that the patient's symptoms are really due to thyroid lack. When this has been established, we can replace the deficit by administering thyroid hormone in the form of thyroid extract. Remember that we are replacing a glandular deficit rather analogous to insulin deficit in diabetes. In treating a new patient, to whom thyroid was administered by another physician, and who is found to be euthyroid at the time you withdraw thyroid, you must be prepared to follow him closely, because he may very possibly become hypothyroid. The circumstance is analogous to withdrawing insulin prescribed by another physician in a patient with a diagnosis of presumed diabetes. The dose of thyroid extract required by the hypothyroid patient is that which is necessary to produce the desired metabolic effect and this is determined by laboratory and clinical examinations. It should be emphasized that patients who have been hypothyroid or myxedematous for a long period of time are extremely sensitive to the extract and when treatment of myxedema of long standing is begun, the initial dose should be rather small and the succeeding doses gradually increased as the patient's circulatory apparatus adapts to the increasing load.

MODERATOR JAILER: Dr. Grumbach will you briefly discuss the treatment of hypothyroidism in children?

DR. GRUMBACH: There are two firmly established indications for thyroid medication during childhood. The first is hypothyroidism and the second is goiter, which in some instances is accompanied by a deficiency of thyroid hormone. Thyroid therapy in infants and children with hypothyroidism produces rapid and dramatic changes. Early diagnosis of congenital hypothyroidism and the prompt institution of adequate thyroid therapy insures a very favorable prognosis for normal somatic growth and maturation and an excellent chance for the infant to attain a reasonably normal mentality. Recognition of congenital hypothyroidism is necessary in treatment of this disorder and this requires a high index of suspicion. We do not have time to discuss the diagnosis of this condition but the picture may be that of a completely athyrotic cretin with onset of symptoms during the first months of life and the classic text-book picture of the disease, or it may be a more subtle disturbance, with an insidious onset, often without conspicuous myxedema, and with retarded growth and development as the most prominent feature. This latter form is often accompanied by a small degree of residual thyroid function.

The importance of early diagnosis and prompt and adequate treatment is most apparent in the effect on mental development. In a recent study by Smith, Mosier and Wilkins in which these and other factors were considered, it was shown that the earlier the treatment was instituted the better in general the mental prognosis and the less the neurologic residua. However, the prognosis for mental development must always be guarded even when therapy is instituted early, since mental development is severely impaired in some infants even when treated early. It is our notion, based on the fact that mental retardation can result from various forms of congenital hypothyroidism (sporadic, endemic, or goitrous cretinism) and the results obtained from studies of placental transmission of thyroid hormone, that the mental retardation in some cases may be due to deficiency of thyroid hormone during fetal life as well as in the postnatal period. The contention that the mental deficiency is related to an associated developmental defect of the brain appears unlikely. Thus early and adequate therapy is of prime importance.

What is adequate thyroid treatment in infants and children? It is

astonishing that a standard and excellent text on pharmacology and one on thyroid disease recommend a dosage schedule which is inadequate. Desiccated thyroid USP is a satisfactory form of therapy. In patients under six months of age, treatment is instituted with ¼ grain a day. While it takes about two weeks to achieve maximum effects, signs of toxicity usually are manifest within four or five days, and in these infants, in order to reach optimal levels of treatment as promptly as possible, we increase the dosage every four to seven days by ¼ to ½ a grain. The optimal dosage in this age group is usually between ¾ and 1½ grains. Therapy must be guided by improvement in the physiologic defects associated with this disease and assayed by the rate of growth and by bone maturation. There is a lag in the effects of thyroid on the bone maturation of about three to four months.

In the older infants therapy can usually be started with ½ grain and increased to 1½ grains at periods of approximately one to two weeks. In toddlers and in school children the optimal dose is somewhere between 1½ and 2½ grains. In our experience it has never been necessary to prescribe more than 3 grains of thyroid to any child with a thyroid deficiency to achieve an optimal response.

Estimation of serum protein-bound iodine, periodic roentgenograms of the skeleton for bone age, and assessment of stature are valuable guides to the adequacy of treatment once the physiologic signs of thyroid deficiency have been corrected.

MODERATOR JAILER: Thank you, Dr. Grumbach.

I should like to discuss some of the other more commonly occurring disorders of the endocrine glands. I must apologize for Dr. Buxton's absence and I should like first to discuss hypogonadism in the female. The most common symptom of ovarian hypofunction is amenorrhea. It is absolutely impossible to discuss the treatment of secondary amenorrhea without knowing what the cause of it is.

Secondary amenorrhea may be due to the menopause. It must be borne in mind that waning ovarian function is a physiological phenomenon and not necessarily of a pathologic nature. Many signs and symptoms usually associated with the menopause may occur in women five to ten years before the cessation of menstrual periods or may occur as late as ten to twenty years after the cessation of the menstrual periods. The cause of the hot flashes, dizziness, lassitude, etc., are really not known. It had been thought that these might be due to increased gon-

adotropin secretion by the pituitary gland which occurs at this time but we have seen the same hot flashes occurring in patients who have been hypophysectomized.

As for the treatment of the menopause, the great majority of women with cessation of menstrual periods require no treatment at all. It has been the experience of Dr. Buxton and his colleagues at the Sloane Hospital in a large series of clinic patients complaining of menopausal symptoms that non-specific sedatives were sufficient to alleviate the symptoms in something like 70 per cent of the patients. We must bear in mind that women in this age group may be susceptible to certain neoplasia. Although there is no absolute evidence that the estrogens may cause neoplasia I hesitate to administer estrogens to women in this group, especially women who have a family history of breast carcinoma. The estrogens may not initiate breast carcinoma but we certainly know how they can effect growth of breast carcinoma in this age group. There is also some correlation between endometrial carcinoma and granulosa cell tumors of the ovary. Estrogens may affect endometrial carcinoma as well.

As far as I can determine, and I think Dr. Buxton would agree on this, there is no need for the parenteral administration of estrogens. We have available substances such as stilbestrol, estrone sulfate and ethinyl estradiol which are as effective by mouth as the "naturally occurring" estrogens given parenterally.

As for the treatment of secondary amenorrhea: If there is sufficient estrogen being secreted by the ovaries, the administration of an active progestational preparation will result in withdrawal bleeding. If no menses occur, one must conclude that ovarian activity is deficient even in the estrogenic sphere. The institution of artificial cycles is quite simple but tells nothing of the underlying difficulty. An attempt should be made to ascertain the reason for the amenorrhea by the use of the various endocrine diagnostic tests available.

As far as the treatment of male hypogonadism is concerned, it is well to consider that the range of variability for puberty runs from 9 to 16 years of age. The great majority of boys in this age group who have not as yet matured sexually will do so spontaneously, if left alone. However, we do have laboratory methods of differentiating eunuchoidism from delayed puberty and before any treatment is instituted. It is the responsibility of the physician to make a diagnosis by available means.

We have available very potent androgenic substances for the treatment of male hypogonadism. We have testosterone propionate which must be given three times a week intramuscularly. We have an oral preparation of testosterone, methyl testosterone which is not quite as effective as the intramuscular variety and must be given in dosages of approximately 25 mg. a day. One should watch for jaundice. Cases of a cholangitic type of jaundice occurring with methyl testosterone have been reported, similar chemically and clinically to the type of jaundice we now see with chlorpromazine. In addition, some of the pharmaceutical companies have prepared long-acting androgenic preparations, the cyclopentopropionate, the caproate preparations, which need not be given more often than once every two weeks or once every month. In addition, too, testosterone may be given by pellet implantation, so that the material need only be given once in six months or once a year. I have had no personal experience with this procedure so I can give very little information about it. Testosterone can also be given by buccal administration but in our experience at least, I think the absorption through the buccal mucosa is spotty and irregular and I do not think it is too effective when administered in this manner.

There are other more serious but less common diseases of the endocrine glands that we as internists deal with. Adrenal insufficiency, for example, is becoming more and more common, since we are diagnosing it at a much earlier stage and also because our surgical colleagues are producing it for us in patients with advanced breast cancer. The mainstay of treatment of adrenal insufficiency or Addison's disease is cortisone. We still have some patients in the Endocrine Clinic who are being maintained on desoxycorticosterone and they are doing pretty well. We just have not switched them over to cortisone as yet. Patients with adrenal insufficiency require small doses of steroids for maintenance as contrasted with patients with the so-called "collagen diseases". We can maintain patients with as little as 10 to 25 mg. of cortisone a day given orally. In addition, about two-thirds of our patients with Addison's disease—and I think this is due to the fact that these patients have varying remnants of adrenals—require in addition to the cortisone a more potent mineralo-corticoid. We can still use desoxycorticosterone acetate, which is given by injection, 1 to 5 mg. per day. For this preparation I do not recommend the buccal route because of the unreliability of absorption. We also have available a long-acting desoxycorti-

costerone, the trimethyl acetate with which patients can be maintained very nicely on but one injection of 25 mg. once a month. DOC pellets can be implanted and usually it takes about one 75 mg. pellet to replace one mg. of DOC daily. In other words, the patients are first regulated by the intramuscular injection of DOC and then if the patient requires, 2 mg. of DOC, then two pellets can be given.

However, we now have available a potent mineralo-corticoid, which can be given orally and consequently is much easier to handle. The dosage can be regulated very easily. This compound is 9-alpha-fluorohydrocortisone, and in our experience dosages between 0.1 and 0.5 mg. per day will adequately maintain the electrolyte metabolism in these patients. This is in addition to the 10 to 25 mg. a day of cortisone. Of course, one must remember that no endocrine preparation initiates metabolic functions in the body. They either accelerate or slow down. Consequently, in order for these mineralo-corticoids to act there must be a certain amount of salt available and consequently we add salt to the diet.

Some questions have been submitted for the panel to answer. The first question, for Dr. Grumbach, is: How many courses of hormone therapy should be given in cryptorchism and how much time should elapse between the courses of therapy?

DR. GRUMBACH: Personally I have had a very limited experience with hormone therapy in this condition, and the results have been, in general, unsatisfactory. Most observers agree that those testes which descend with this treatment, would have migrated into the scrotum spontaneously at puberty. There is now available a potent preparation of chorionic gonadotropin which contains 20,000 units in 10 cc. In the patients with bilateral cryptorchism in whom we use this treatment, it is employed according to the recommendation of Engle and Robinson, that is, 4- to 5,000 units daily intramuscularly for three days. If descent does not occur in 7 to 10 days, orchiopexy is performed.

MODERATOR JAILER: May I add that I think chorionic gonadotropin is used in cryptorchism as a diagnostic procedure rather than for treatment. One course of treatment is usually sufficient; whether it be the short high dose regimen or the prolonged regimen. Each has its advantages and disadvantages but the point is that if the testes descend as a result of this hormonal treatment, one can then be satisfied. We know therefore that these testes are really not cryptorchic but of a retractile

type and that at puberty when they get larger they will remain in the scrotum. Dr. Engle demonstrated this a long time ago in the monkey. The monkey has retractile testes until puberty. When he administered chorionic gonadotropin to immature animals a descent of testes occurred and they remained scrotal as long as he administered the chorionic gonadotropin. I think these are comparable situations. Administration of APL (chorionic gonadotropin) is used as a diagnostic test. Would you agree with that?

DR. GRUMBACH: Yes, with the addition that those testes which do not descend under the influence of the boy's own gonadotropin at puberty rarely respond to the administration of exogenous hormone. This applies especially to the unilateral undescended testes.

MODERATOR JAILER: The time for orchiopexy is a matter of dispute. I myself have not had too much experience in this field but I know that Dr. Robinson and Dr. Engle believe that the earlier the orchiopexy is done the better is the prognosis as far as spermatogenesis is concerned. However, this is not necessarily the final answer. There are several series which disprove this so we must just wait until more information is available from adults who had their orchiopexy done in childhood.

There is a question here relevant to the treatment of the hypogonad, the obese boy of 15 with descended but small testes. I do not think that a fat boy of 15 who has a small penis and small testes is necessarily hypogonad. This may be merely a matter of delayed puberty. As you know, eunuchoidism can vary, starting from complete atrophy of the testes, to the extreme where there is no evidence of lack of androgens but with tubular fibrosis of the testes. These variables have been lumped together into the so-called Klinefelter syndrome. Laboratory tests made at age 15, should be able to establish a diagnosis of hypogonadism. In a 15 year old boy with hypogonadism the gonadotropic titer of the urine is usually elevated, whereas in the patient manifesting delayed puberty practically no gonadotropin would be found. If one permits the great majority of these fat boys to go untreated and if they can be made to lose a little weight, a gratifying transformation into sexually mature young adults can be observed. The so-called "Froelich's syndrome" should not be used at all in describing these fats boys.

I thought we would get some questions on the thyroid. The first thing I would like Dr. Aranow to discuss is the so-called syndrome of metabolic insufficiency. A pharmaceutical company, which shall remain

nameless, has been advertising a new syndrome of metabolic insufficiency in the presence of normal thyroid function. Oddly enough this syndrome does not respond to the usual thyroid extract but responds to the particular product of that company. I would like Dr. Aranow to discuss that.

DR. ARANOW: The existence of a possible endocrine block in the utilization of thyroid hormone has been made clear by the experimental discovery of the fact that triiodothyronine is a very potent metabolic agent. It has calorogenic actions and it can cure all of the manifestations of myxedema. It is found in the thyroid gland, in small quantities, and in the blood and it seems possible to conceive of situations in which the individual would not be able to change thyroxine into the presumably active cell level metabolite triiodothyronine. This hypothetical possibility has been blown up, in my opinion, to proportions far beyond those which are justified by the evidence. The syndrome described, and I just happened to have some of the advertising literature, is similar to the syndrome which has been described in another entity, hypoglycemia, in which I have been interested. It is also similar to the syndrome which has been described by other enthusiasts in chronic brucellosis, tired people who just seem not to like the way life is. In general they tend to have rather low basal metabolic rates. They are inflexible, without ambition. Their behavior suggests that life is not very much fun for them. In general, these people don't respond to thyroid extract and in a small number of cases cited in the literature they are reported to respond well to triiodothyronine. This potent calorogenic agent can, when given in sufficiently large doses, raise anyone's metabolism. It raises it so rapidly that possibly some of the normal compensatory mechanisms of the body, which have time to take over and to maintain homeostasis when the long-acting thyroid is given, don't have a chance to come into play. When a person, whose metabolic rate is perhaps properly situated at −25 is given low but increasing doses of thyroid extract when he does not need them, decreases his own endogenous production, at the end of a few months he still will have the same level of circulating protein-bound iodine. When triiodothyronine is given, his body has not time to make the changes and his basal metabolic rate is elevated. In my opinion, psychotherapeutic factors may be the major ones in some of these patients, since many of these patients report improvement. It is worthy of note that sometimes this improvement

has not been maintained. Although this endocrine block may exist in a rare case, it is my impression that the symptom complex now publicized as metabolic insufficiency and said to be common, is probably a rare clinical entity.

It is also worthy of mention that if these patients are unable to metabolize thyroid hormone at the tissue level, one would expect that their thyrotropic hormone would be gradually increased, as it is in individuals who are thyroidectomized. One would also not expect to see toxic symptoms because of thyroid extract; why should thyroid produce toxic symptoms without producing other metabolic effects? I might say I regard the syndrome with skepticism, although not a closed mind.

MODERATOR JAILER: Another point I should like to make, Dr. Aranow, is to advise caution in the use of such a potent and fast-acting thyroid hormone. In the presence of myxedema we have always recommended the administration of small doses of thyroid, increasing in small increments over periods of time.

If one should start, especially with someone in the older age group, with doses of a fast-acting potent thyroid hormone, I think we may get into trouble, particularly in the cardiac sphere.

DR. ARANOW: I would certainly agree with that,—one can experimentally raise the patient from myxedema to euthyroidism in one day with triiodothyronine. What this will do to the vascular system is not hard to imagine.

MODERATOR JAILER: *Dr. Aranow, will you comment on the comparative value of surgery and radioiodine therapy in patients with toxic multinodular goiter?*

DR. ARANOW: I will tell you that this is largely a matter of opinion based on the malignant potential of multinodular goiter. In this very building I heard a very heated discussion by some rather distinguished men regarding the possible appearance of carcinoma in multinodular goiter indicating that this is a field in which the differences of opinion are considerable and in which emotions tend to run high. In general statistics appear to indicate that carcinoma of clinical significance in patients with thyrotoxicosis is rather rare, whether or not they have diffuse or nodular goiter and I think that in the older group one is justified in treating these people with radioactive iodine, even though, not infrequently, greater amounts of radioactive iodine than commonly

used are required. People who believe that we may be treating patients with the hyperactivity in the diffusely hyperplastic tissue in the presence of non-functioning nodules will worry about the malignant potentiality of this so-called cold or non-functioning nodule.

MODERATOR JAILER: *Dr. Grumbach, I have two separate questions and our time is short. I wonder if you could go through them very quickly. One, what is the value of appearance of ossification centers of the wrist bones in children as a guide to the diagnosis of hypothyroidism; and two, how do you diagnose infantile hypothyroidism?*

DR. GRUMBACH: There are many factors which can cause retardation of skeletal maturation and there are many disorders in which assessment of skeletal maturation by roentgenograms of the wrist show retardation. This finding does not establish by any means the diagnosis of hypothyroidism. In normal children the maturation of the round bones in the wrist may be delayed in comparison with the rest of the skeleton. We believe that an estimate of the number of centers in one half of the skeleton, particularly in children under the age of three years, gives a more accurate approximation of the bone age. At best, determination of bone age is an imprecise procedure. Many children are needlessly treated for hypothyroidism simply because the development of the bones of the wrist is delayed. This is only one feature of hypothyroidism and there are others which should be detected. In addition to stunted growth and an immature appearance, one must look for the physiologic signs of thyroid deficiency such as diminished activity and torpor, circulatory changes, cool and thickened skin, hypotonic muscles, constipation and, in younger infants, feeding difficulties and respiratory distress. Then we must confirm the diagnosis by obtaining either a serum protein-bound iodine or a radioactive iodine uptake. Anyone can obtain a serum protein-bound iodine determination. There are laboratories which perform this test accurately in this city and in other parts of the country. Before any child is put on thyroid therapy for hypothyroidism an attempt should be made to document the diagnosis and it should not be based simply on a delay in skeletal maturation. In fact, in instances of hypothyroidism of the congenital variety, skeletal maturation is not delayed one to two years but it is severely delayed and it is more delayed than the retardation in height. Many healthy children whom we see have a bone age which varies from one to two years on either side of the chronologic age.

MODERATOR JAILER: Thank you.

The next question is: What is the present status of the relationship of endocrinology to acne vulgaris?

DR. ARANOW: The only thing that makes people believe there is one is that it appears with administration of testosterone. We see it in adolescence. Therapeutically this has not been established.

MODERATOR JAILER: *The last question: How do you treat symptomatic osteoporosis?*

As you know, Fuller Albright did much work in this field. He believed that osteoporosis was primarily a disease of protein catabolism of the bony matrix, thereby secondarily pulling out calcium from the bones. This has been disputed more recently. There are those who claim this is not so, that osteoporosis is primarily a disease of calcium and not of protein. We do not know the correct answer at the present time. I would think though that we should continue to treat symptomatic osteoporosis very similarly to the way Albright suggested six or seven years ago. We like to give a high protein diet in an attempt to have protein available and then give one of the anabolic steroids, a steroid which will tend to put the patient into a positive nitrogen balance. Testosterone is one such preparation but if given to a female one must be prepared to pay the price of side effects, including some degree of virilism. One can also give estrogen. Albright thought the two given together potentiated each other but, remember, they do not cancel each other out on physiological effects. The androgen has its physiological effects and the estrogen has its physiological effects and one must also pay the price of estrogen administration, especially in a post-menopausal woman. One may get into difficulty with vaginal bleeding and have a sense of insecurity in not being certain whether the vaginal bleeding is due to the administered estrogen or to carcinoma in the uterus. We also like to administer a fairly high calcium diet.

I wish to thank the panel members for their presentations and the audience for its attentive interest.

THE SIGNIFICANCE TO MEDICAL HISTORY OF THE NEWLY DISCOVERED FOURTH CENTURY ROMAN FRESCO*

CURT PROSKAUER, D.M.D.

Curator, Charles H. Land Museum, Columbia-Presbyterian Medical Center, New York, N. Y.

NEARLY two years ago the Secretary of the Pontifical Commission of Sacred Archaeology, Reverend Father Antonio Ferrua, of the Society of Jesus, announced in *L'Osservatore Romano* that a Christian cemetery, hitherto unknown to scholars, had been discovered beneath the Via Latina, the modern Via Dino Compagni, in the south-eastern part of Rome. The correspondent of *The New York Times*, Mr. Arnaldo Cortesi, reporting this important discovery, observed that this catacomb was remarkable for the number and beauty of its frescoed paintings. He quoted Father Ferrua, who had directed the excavation, to the effect that "nothing like this has ever been found in any early Christian cemetery. The frescoes represent a wide variety of subjects, some from the Old and New Testament, but some are frankly pagan. Others represent *scenes of life at the time when the catacomb was decorated*." The correspondent added that Father Ferrua attributed the catacomb to the early fourth century, and remarked: "*The archaeologists made no effort to hide their amazement at finding such subjects chosen to embellish tombs of the early Christians. Scenes from the contemporary life of ancient Rome include portraits of famous physicians adorning the tomb of a surgeon. The surgeon himself is depicted performing an operation.*" (Figure 1.)

Some days later *The New York Times* published the photographs of two frescoes in the newly discovered catacomb, one of them captioned "*A Roman surgeon is shown during an operation as colleagues look on. This fresco adjoins the surgeon's tomb.*"

When I saw the picture of the "surgeon during an operation", I thought at once of the miniatures to be found in medieval manuscripts

* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 22, 1958.

Figure 1.—Fresco in the newly discovered catacomb in Rome. Fourth century A.D.

and the many woodcuts in printed Renaissance books representing anatomy teachers dissecting human bodies for purposes of instruction (Figures 1, 3, 4, 5). In all these pictures the professor is seated or standing on a raised platform or in some other prominent position, reading the words of some medical classic or quoting them from memory; the dissector is performing the actual operation, and the ostensor or demonstrator is pointing with his baton to the particular organs or parts of the body which the professor is discussing.

The fresco of the so-called surgical operation has all the regulation performers of a medieval dissection: the lecturing professor is the large dark central figure surrounded by his students, the ostensor is pointing his rod at the cadaver lying in the foreground, while the dissector is not present, having already done the actual cutting-up and withdrawn.

I never for a moment imagined that this fresco could represent a

Figure 2.—Sacrophagus of a Roman-Christian Physician. Fourth century. (Metropolitan Museum of Art, New York, N. Y.)

surgical operation, since surgeons at that time dared little: they restricted themselves to external operations, performing hardly any internal surgery. In any event, it would have been impossible to open the abdominal cavity of a patient as wide as shown in the fresco without killing him. An important additional point is the fact that not one of the many persons represented in the fresco shows the slightest interest in the treatment being given the "patient", who would have bled to death very quickly with that open abdomen. If the professor were demonstrating an operation, he would not be sitting in the background, but would be close to the patient while operating, whereas if the scene depicts a dissection for teaching purposes, a lesson in anatomy following the actual dissection, the professor's place may be in the background. We have learned from many later representations of dissections in the late Middle Ages and the Renaissance, that with time the professor is more and more removed from the subject of his study,

Figure 3.—Miniature in a work of Avicenna. Manuscript, 15th century. (Glasgow. Ms. Hunter 9, fol. 10.)

ascending his high professorial "chair" in the literal sense of the word.

Dr. Frederick A. Mettler, historian and Professor of Anatomy, Columbia-Presbyterian Medical Center, has been kind enough to call my attention to another important fact confirming this interpretation of the fresco: the body at the lower left corner has clearly protruding ribs, a phenomenon found only in corpses already dried up, resembling the skeletons always presented in the so-called Totentänze—dances macabres.

Art historians and historians of medicine are familiar with the graphic tradition that began in early antiquity and continued into the 16th, in some cases even into the 18th century. We find this tradition not only in general art, but also in medical representations, anatomical

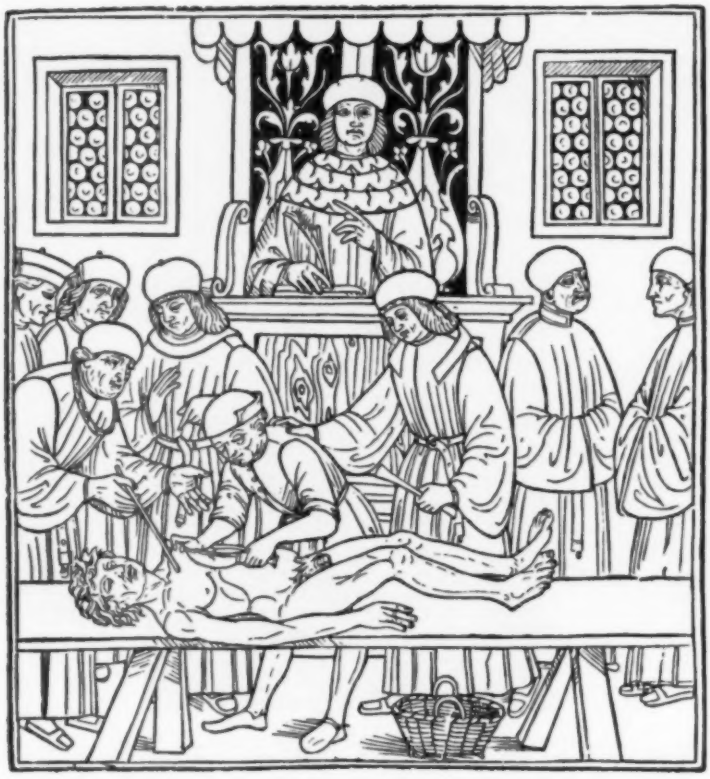

Figure 4.—Dissection scene in Ketham, Fasciculo medicine, 1493.

drawings, pictures of the fetus in various positions and representations of surgical operations and anatomical dissection scenes for teaching purposes.

We should also bear in mind that the artists of the Middle Ages often made use of symbols, a kind of sign language understood by their contemporaries, or at least their educated contemporaries. Thus a rod in the hand of a man pointing to an opened body before an audience may have served to announce that the artist was depicting a dissection. However, I should not pass over in silence a fact known to every child, that miracles recorded in the Old and New Testament were performed with a rod, so that it is quite understandable why our

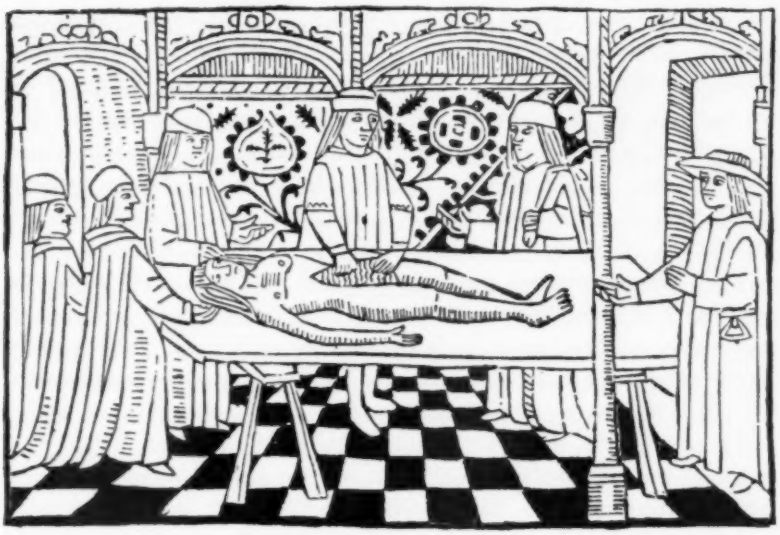

Figure 5.—Woodcut in Bartholomaeus Anglicus, De proprietatibus rerum. Toulouse, 1494.

fresco was later interpreted as we shall see, as the representation of a miracle; understandable, however, only if all the other requirements for such a hypothesis are fulfilled.

I informed *The New York Times* of my interpretation, which differed from that of the caption provided by The Associated Press; I added that this fresco had great importance for the history of medicine because it is the earliest known pictorial representation of a dissection before a medical class, dating from the fourth century of the Christian era and thus offering visual evidence that medical dissections of human bodies for teaching purposes were performed nearly a thousand years earlier than had been believed heretofore. According to the archives of the University of Bologna, the first documented dissection for teaching purposes was performed in Bologna in 1281.

Newspapers—*The New York Times* first of all—and scientific journals in various fields, in archaeology, history of art and history of medicine, made this newly-discovered catacomb fresco widely known to the general public and to scholars. Very soon a controversy arose as to the interpretation of this fresco as an anatomical dissection.

Most differences of opinion developed concerning identification of the central figure, which variously was called "Christ the Physician teaching directly from the open cadaver," "Christ in the midst of his Apostles," "Christ the Healer," and "Christ resurrecting the dead" or, the body in the foreground, called "Judas, whose body opened and whose intestines fell out when Christ was resurrected." The most recent identification was published in the *Rheinischer Merkur* by the eminent medical historian Professor Walter Artelt, Director of the Institute of the History of Medicine at the University of Frankfurt am Main. He says the fresco represents the resurrection of the bones in the Valley of Dry Bones, predicted by the Prophet Ezekiel. Artelt argues ingeniously, supporting his contention with pictures of sculptures on sarcophagi representing the Ezekiel story. He has been kind enough to mail to me the original photographs. I believe that in many important points our fresco fails to meet the requirements of the Ezekiel story, but I feel I am not sufficiently unprejudiced or competent to decide this question. I therefore leave the elucidation of Artelt's interpretation to experts in the history of art, especially Christian and medieval art.

My chief *general* argument against all these biblical interpretations of the fresco is that if there were the slightest possibility of their accuracy, a high officer of the Vatican, a specialist in Sacred Archaeology and Art, would never have stated that the scene on the fresco is a medical scene—I quote Pater Ferrua: "The surgeon himself—whose tomb is in the catacomb—is performing an operation." But to make sure that the central figure did represent a surgeon and not Christ or any other figure or event from the Old or New Testament, I consulted some Christian Art and Archaeology and Medieval Art experts; these experts, with the exception of Father Ferrua, are kindly participating in this symposium, to help clarify all questions of art connected with the fresco.

The very title of this symposium, "The Significance to Medical History of the Newly Discovered Fourth Century Roman Fresco", takes for granted that the fresco, found in a Roman catacomb, represents a medical scene. But for this concept we need historical and medico-historical support in addition to the evidence we have from the art experts' view-point.

The painting exemplifies the classical style (Figure 1) of late Roman and early medieval art, the symmetry and the two-dimensional surface,

which does not fail completely, however, to give some impression of perspective, achieved by depicting some of the figures at a distance, and others closer, overlapping each other.

We do not know and will certainly never know why a dissection scene should have been painted on the wall. Had the practice of dissection made such a sensation that they wanted this fresco as documentary proof, a sort of painted chronicle for posterity much like our foundation corner-stone where we deposit significant products of our own age? Or was the surgeon presiding in the picture so eminent that his family or his students ordered the painting as a memorial on his death and burial in this catacomb? Or it may not be a poor guess that the anatomy lesson depicted was the first one of its kind at that time and the surgeon performed the dissection in the catacomb so that he would be safe against surprise in case the performance should arouse the indignation of the common people.

All the figures wear the himation, the long white garment of the learned, the very same dress we find (Figure 2) on the sarcophagus of a Christian-Greek-Roman surgeon, also dating from the fourth century, and on the funerary monument of the Athenian physician Jason, dating from the second century, so that we can conclude with some assurance that the central figure in the fresco is a Roman physician and the younger men around him are his medical students. In Rome of the fourth century A.D., among diverse types of medical education the most popular was the apprenticeship we see pictured here. At that time there was in Rome no special medical school—like the late medieval and early Renaissance schools of Salerno, Paris, Padua, Bologna, Montpellier; medical students simply came together at the house of some eminent practitioner they had chosen as their teacher, and they received their training in the so-called "medicatrina". Anatomical knowledge at the time of Galen—who flourished about half a millennium before the catacomb was built—had been based on animal dissection—pigs, sheep, oxen, cats, and dogs. Galen's favorite victim was the Barbary ape, or some other type of macaque. Belief in magic, fear of corpses, a certain revulsion against dissection of human bodies prevailed among all ancient peoples, who regarded any act of violence upon the body as odious. We know, however, that dissections *were* performed; it was the scholars, with their spirit of inquiry who did them. A scholar's ideas may be altogether unrelated to those of the laymen of his era. The opposition to

dissection, then, may have prevented the scholars from gaining access to cadavers, but it would have been as possible to overcome opposition at that time as it was during the Renaissance, when Vesalius cut a hanged criminal down from the gallows to dissect him, or as it was as late as 1788 in New York, when a riot broke out on the discovery that the grave of a woman recently dead had been opened and the body taken out of the casket and used for dissection.

We have no documentary proof as to whether or not human dissections were performed in Rome between Galen and the time of our fresco. Those who maintain that it would have been impossible to perform a human dissection in the fourth century and still more impossible to advertise such a performance in a Christian catacomb, refer to the opposition of the Church which—as they believe—hindered human dissection during the Middle Ages and hence the development of the science of anatomy. This error springs from the fact that much later—to be exact, in 1300, 1000 years after our fresco was painted—Pope Boniface VIII issued a bull, *De Sepulturis* (Sepultura more teutonico) forbidding, on pain of excommunication, a practice which had spread during the Crusades: the separation of the flesh from the bones of persons who had died abroad; this process involved boiling and dismembering as a preliminary to storing the bones in jars for transportation back home from the east, for burial. No body so treated was to be buried in consecrated ground. The Pope's objection to the practice was that it was cruel, inhuman and barbaric. Dissection of the human body was never, however, officially forbidden by the Church. Perhaps another reason why some believe human dissection was impossible during the Middle Ages, is that "the Church abhors the shedding of blood" (Ecclesia abhorret a sanguine). In fact, again nearly 1000 years after our fresco—in 1162—the Council of Tours forbade the *clerical orders* to perform surgical operations, but did not forbid surgeons or physicians.

There is nothing in Church Law, or in any Papal bull which treats of the resurrection of the body in connection with dissection. Had dissection of the human body been considered an offense, this should have appeared in the handbooks of penance. Nothing on this is to be found there. The truth is that all these events have become mixed up in people's minds with relation to their time, the persons concerned, and the real meaning of the decrees, so that erroneous arguments have been used and erroneous conclusions drawn. We know that in the late Middle

Ages public human dissections were performed in Montpellier by the medical faculty; these were very popular shows, not only for the medical students, but also for the various social sets of the city. Dignitaries and high officials, upper class women, even clergymen, made up the audience at these demonstrations, usually given in a large hall or in the open-air, as you can see from the miniature of a manuscript of the Canon of Avicenna (Figure 3).

"What is a dissection scene doing in a Christian catacomb?" This question, hinting at the absurdity of so interpreting a painting in a catacomb, has been asked several times and always with it has been the remark that the walls of a Christian catacomb could not possibly be adorned with such a secular, worldly painting. This view-point is obviously wrong. If it had been impossible thus to decorate the walls of a Christian catacomb, if it had been contrary to the rules of the Christian Church of the fourth century and offensive to Christian feelings, Pater Ferrua, whom I must quote again, would have been the first to say so. Besides, the facts speak against this contention. Along with testimony to age-old Catholic beliefs, the catacombs have yielded up a wealth of pagan and secular art. In addition to scenes from the Old and New Testament, we find scenes from Egyptian and Greek mythology which could easily offend orthodox Christian feelings; we find above all, distinctly worldly scenes, for example, in the catacomb of St. Domitilla in Rome, a fresco of a grain market, with warehouses and workmen unloading barges on the Tiber; in the catacomb of the Church of St. Pudenziana, a street scene which may be Rome of about 390 A.D.; in other catacombs, frescoes and sarcophagi with a flowergirl behind her flowerstand, eight men working at large tubs, a smith at the forge, a carter with his team of horses. In the grotto tombs beneath the Church of St. Peter there are frescoes of dancing figures, an Egyptian divinity, Bacchic rites, and one showing the steward of an estate checking over accounts with an underling, a very worldly scene indeed.

When we think of Christian catacombs, we think instinctively of an exclusive religious place, of a subterranean prayer and hiding place from persecution, besides its destination as a burial place to be used for religious purposes only. This, however, is an erroneous concept. The catacombs were, besides the already mentioned purposes, like the churches of today, places for social gatherings. In later times—the time of the fresco—when thousands of pagans were admitted to the Church,

the agape, the brotherly love and charity feast, became frankly a pagan festival, a kind of picnic to which the parishioners arrived with baskets of food and wine and sat up all night, passing round the bottle. One of the pilgrims scribbled on the wall of a catacomb: "I, Tomius Coelius partook of a refreshment-meal for Peter and Paul." When St. Augustin —just at the time of the painting of our fresco—saw such scenes, he cried: "The Martyrs hear your bottles, the Martyrs hear your frying-pans, the Martyrs hear your drunken revels."

It is apparent that the findings in the catacombs indicate that they were not only the world of the Martyrs, but also places for daily life; therefore it would not have violated religious feelings too much to see a painting there representing an anatomical dissection scene.

If the reasons I have given for my interpretation of the fresco are sufficient, and if the arguments brought forward in opposition are proved untenable, the fresco is our first documentary, visible proof that human dissections for teaching purposes were still, or again, performed in the fourth century of our era. It will mark a great advance in our knowledge of the history of medicine, especially of the development of anatomy, concerning which we have neither pictorial nor written evidence for the first ten centuries A.D. It will enable us to trace human dissection back a thousand years. One of the foremost historians of anatomy, Professor Charles Singer, has written me a letter in which he offers as a reason for his doubts that the fresco is a dissection scene: ". . . to find a dissection scene that could be firmly dated to the fourth century would be about as revolutionary as finding a Ruhmkorff's coil from the eighteenth century. The whole of medical and scientific history would have to be rewritten if this were so. Of course, revolutionary historical discoveries do occasionally turn up." I hope one just *has* turned up.

Scholars may not be always free from preconception when it comes to evaluating what they have never seen or heard of before. The interpretation of new material always provokes discussion, unless it is quite obvious.

I have been able to give you only a summary of everything I should have liked to tell you about this fresco. I am sure, however, that the distinguished experts in medical history, anatomy, history of art and archaeology, as well as in the history of the period when this catacomb was used, will add much valuable and decisive information, so that you

will be able to judge whether or not I am correct in regarding this fresco as a representation of an anatomical dissection for teaching purposes, and consequently, whether the fresco has the great significance for medical history which I have assigned to it.

DISCUSSION

GEORGE W. CORNER—*Historian, Rockefeller Institute for Medical Research, New York, N. Y.*

I agree with Dr. Proskauer that the catacomb painting represents a medical teacher presiding over a demonstration. The arrangement of the figures and the details confirm his view to that extent. The resemblance to anatomical dissection scenes painted a thousand years later does not prove however that human dissection was practiced at Rome in the Fourth century A.D. Although we have no written evidence from that immediate period, Galen and Celsus have left us from the first and second centuries clear statements to the contrary. There was, however, another kind of anatomical and surgical teaching, described by Celsus in *De Medicina,* Book 1, 25, where he points out that much may be learned by observing internal structures which are exposed in persons who have suffered severe wounds. In my opinion the scene we are discussing represents just such an anatomical-surgical demonstration upon a gravely wounded patient.

The scene however appears not to be literally represented. The central figure drawn larger than others, as if to emphasize his importance, is dressed in the old greek *himation* whereas the pupils wear togas. The central figure, is in fact quite similar in pose, features, and costume, to the Greco-Roman god of medicine Aesculapius as figured in numerous temple statues of the period. I suggest that the picture is an idealized representation of some celebrated doctor, surrounded by his pupils, and shown in the guise of Aesculapius to symbolize his eminence as teacher and physician.

LOREN C. MACKINNEY, Ph.D.—*Kenan Professor of Medieval History, University of North Carolina, Chapel Hill, N. C.*

In a humorous vein Dr. Walter Artelt of Frankfurt recently wrote me as follows: "In 1956 a Roman theologian (Father Ferrua, S.J.) rolled a corpse over the fence of Christian archeology into the garden of medical history. . . . The medical historians were bewildered. . . . One of them, from the Academia Medicinae Novae-Eboracensis (Dr. Proskauer) said it is a *dissected anatomical body.*" Apropos of this opinion, another medical historian, Dr. Corner, considers it a *chance anatomical body.* Still others consider it a *surgical operation.* Dr. Artelt rejects all three medical theories. He continues in his letter: "So bewildered are the medical historians that I have rolled the body back into the garden of the Christian archeologists; it is their body, not ours. . . . Compare it with the pictures enclosed herewith: a body on the ground, and *Ezekiel* with a wand *touching life into the dry bones* (Ezekiel, 37). Does not the catacomb corpse depict the same?"

My friend Artelt's theory does not satisfy me. Neither does another Biblical theory; viz., *Lazarus being raised from the dead*. Therefore I roll the body back into our garden of non-Biblical, medical history. I reject the theory of surgical operation; there are no instruments. As I see it, this leaves two possibilities, those of Proskauer and Corner. Between them I cannot make a choice until, like doubting Thomas, I see the actual body, in the mural. Meanwhile I assert that it is *not* a precursor of the earliest known dissection illustration (ca. 1300). It is late Roman, not early medieval.

ROSALIE B. GREEN—*Director, Index of Christian Art, Princeton University, Princeton, New Jersey.*

The Index of Christian Art is always pleased at being able to list a new saint or a new scene in its file of works of Christian art dating before 1400 A.D. These files now include over 500,000 entries, illustrated by about 100,000 pictures. Among them, the Via Latina fresco can be termed unique: no parallel to it is known in Christian art.

On the basis of the Index's accumulated knowledge, certain suggestions already made can be eliminated. We can be reasonably sure that the fresco does not represent 1) Ezekiel and the vision of the valley of dry bones, 2) the death of Judas, with his soul escaping through his stomach, or 3) a miracle of Christ. The first two of these as represented in places where no doubt about subject matter exists are incompatible with the Via Latina fresco; and the third is impossible because of costume (Christ is never shown with His breast bared except after the Resurrection) and facial type.

These negative conclusions may help to clear the ground for the correct interpretation of the enigmatic fresco in Rome.

MR. A. HYATT MAYOR—*Curator of Prints, Metropolitan Museum of Art, New York, N. Y.*

If I had been scheduled to talk after Prof. Meyer Schapiro, I could never have risen to my feet, for he, I feel sure, has discovered the meaning of the painting in the Via Latina catacomb. However, since I am asked to write my bad guesses, I will do so, history being mostly a record of errors.

I had two explanations (both wrong) for the painting:

1. In Alexandria about 300 B.C. Greek doctors wrote at length about dissecting men. Their contemporary accounts have disappeared, but were current in imperial Rome, where Galen and Celsus quoted from them, long after the ancients had ceased to dissect human beings. I thought that the Via Latina painting might be a kind of pictorial quotation—possibly even a copy of a lost manuscript illustration—to commemorate dissections made some 600 years before.

2. Galen says that when he was young he attended a corps of gladiators as their resident surgeon, a surgeon being as necessary to gladiators as a bonesetter is to a football team. He also says that he got to know bits of human insides through chance wounds, and he must have had many such instructive glimpses when his gladiators briskly vivisected each other.

Now if the opened body in the Via Latina painting could be a dead gladiator, this might, I thought, explain why the dissector has apparently left the room, for

he would be out in the middle of the arena receiving applause. This mistaken hypothesis has, at least, enough ingenuity to amuse.

FRED A. METTLER—*Professor of Anatomy, College of Physicians and Surgeons, Columbia University, New York, N. Y.*

There would appear to be no compelling reasons to require us to accept the hypotheses that the Via Latina fresco represents a surgical operation, that the central figure demonstrates that Christ is a cultural equivalent of Aesculapius or is an attempt at a literal representation of any person buried in the vicinity. That it may be a stylized representation, along Alexandrian traditional lines, of "medicine" as a field worthy of Christian approval, or an indication that one or more followers of the art were buried in the vicinity cannot be denied. The scene itself demonstrates the preexistence of morphologic instruction of a rather superficial type but does not prove the contemporary existence of such a pursuit. The portrayal may be a cultural residue from an earlier period and different location. That the central figure may be intended to represent Aesculapius or Hippocrates is possible but, since no authentic portrayal of such persons real or mythical is identifiable, there is no reason to prefer such an explanation to one which would state that the entire scene represents "medicine" as an abstraction. There is no compelling reason to conclude that this fresco proves that anatomic dissections (in any sense beyond rather simple inspections of material available from fortuitous circumstances) were performed in the fourth Christian century.

MEYER SCHAPIRO, Ph.D.—*Professor of Fine Arts and Archaeology, Columbia University, New York, N. Y.*

The image, with a central seated figure surrounded by smaller figures, does not conform to the types of funerary pictures of deceased persons in their trades or professions as we find them in the catacombs, or to images of groups of doctors and learned men elsewhere. But it resembles closely a familiar fourth century type of Christ among the apostles (catacomb of Domitilla). The central figure in a distinctly Greek costume stands out like a god. The whole is not conceived as an episode from daily life, but as an ideal presentation; the body on the ground appears as a state attribute or symbol.

The main figure suggests the person of Aesculapius, although he lacks the customary staff and serpent. The nude body on the ground recalls the ancient accounts of healing by incubation in the temples of Aesculapius. Inscriptions at Epidaurus describe the patients reclining on the floor of the temple and their visions of surgical intervention by the god and his doctors. The shape of the abdominal cut in the body in the fresco is like the opening with exposed viscera on a terra cotta ex-voto from the temple of Aesculapius in Rome.

A figure in a fresco of another chamber of the catacomb, holding a serpent at her breast and described by the discoverer as Cleopatra—an unlikely identification—perhaps represents Hygeia, the daughter and companion of Aesculapius, although she may be Persephone.

Aesculapius was an important divinity in Rome as late as the fourth century A.D. He had been a patron of a collegium or burial confraternity. His temple on an island in the Tiber was a popular sanctuary and medical establishment,

which was later the site of a church. Venerated as a savior god, as an ethical teacher and worker of miracles, Aesculapius was a serious rival of Christ, like whom he had died and risen to heaven. Christ's miracles correspond surprisingly to those of Aesculapius; the frequency of the phrase "Christ the physician" in early Christian writings confirms this correspondence. Among the Roman emperors of the fourth century, the anti-Christian Julian was especially devoted to Aesculapius. The pagan god could nevertheless be represented in a Christian catacomb like Orpheus or Hercules, another savior man-god whose deeds are pictured in the same catacomb.

In the light of the religion and art of the fourth century, the catacomb fresco may be interpreted as an image of Aesculapian medicine conceived symbolically as a type of deliverance, parallel to other images of salvation in the art of the catacombs, and corresponding in its large form to the pattern of Christ among the apostles in the same art.

REV. JOHN H. HARRINGTON, D.L.S.—*Librarian, Corrigan Library, St. Joseph's Seminary, Yonkers, N. Y.*

The fresco under consideration is either Christian or pagan in origin, and either secular or religious in content. To accept it as a Christian work of religious content is to be faced with something entirely new, and hitherto unknown in Christian iconography. To suggest that it is a medical scene of Christian origin is to encounter some difficulty arising from the lack of medical detail, in the presentation. However, it is possible that here we have the earliest artistic presentation of a medical scene, be it a lesson in anatomy or a surgical procedure. The interest and attainments of Christians in the field of medicine were such at this time (and in the preceding centuries) to render it quite probable that an outstanding Christian surgeon or professor of medicine could be honored or commemorated in this fashion. To accept this work then as a secular scene in a Christian catacomb to commemorate the profession and attainments of a deceased Christian presents no difficulty externally, objections from the Church, opposition of the Church or Christians to medicine, etc. There are some things to be explained internally, lack of instruments and the like, but since this may be the earliest known representation of the subject we have no knowledge of the accepted form or frame of presentation. While we know the later patterns of depicting medical scenes, we have no right to insist that earlier centuries should have known and followed them.

This particular catacomb is not mentioned in the ancient documents and probably was a private rather than a public burial place which served the needs of an entire family, pagan and Christian members alike. In view of the mixture of pagan and Christian burial and art to be found in this catacomb (and others as well), it may be suggested that the fresco under discussion was executed to commemorate pagan members of the family, and took its inspiration from a contemporary cult of strong popular appeal.

There is a great need for extensive and concentrated examination of the physical evidence and until this is done it will not be possible to prefer one suggestion before the other.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting of December 12, 1957, at The New York Academy of Medicine

The In Vivo Removal of Cartilage Matrix by Papain

ROBERT T. MCCLUSKEY

New York University College of Medicine

Cartilage is the simplest connective tissue in the body. More is known of its chemical composition than of any other tissue in the body. Experimental production of *in vivo* changes in cartilage offers a model for a study of the precise ways in which ground substance can be damaged. The widespread *in vivo* removal of cartilage matrix by papain is a change which can be defined on the chemical level.

The intravenous injection of a solution of crude papain into young rabbits resulted within several hours in rapidly progressive loss of rigidity and collapse of the ears. During the following several days, the ears gradually regained their tone and became erect again. The rabbits showed no other ill effects[1].

Histologic examination showed complete loss of basophilia of cartilage matrix in all locations examined which included ear, trachea, bronchi, joints and epiphyses. There was some diminution in the metachromasia of cartilage. During the first several hours, basophilic, metachromatic material accumulated in the connective tissue and lymphatic channels adjacent to cartilage. These findings indicate a liberation of chondroitin sulfate in some form from cartilage resulting in its diffusion into adjacent tissue and removal by lymphatic channels. Recovery of cartilage, as judged histologically, was complete in about two weeks.

There were no histologic changes in tissues other than cartilage. Special study was made of tissues known to contain chondroitin sulfate or other sulfated mucopolysaccharides, such as cornea, heart valves, aorta and skin. No changes in the basophilic or metachromatic staining properties occurred in these tissues.

Chemical analysis of cartilage was performed in this laboratory by Dr. Theodore Tsaltas. He found that 24 hours following papain injection, there was a reduction in the chondroitin sulfate content of cartilage of about 40 per cent. There was an increase in the molar ratio of nitrogen to hexosamine in cartilage, also[2].

In order to study the rate and extent of removal of chondroitin sulfate further, rabbits were given S^{35} several days prior to the injection of papain. It has been shown that most of the S^{35} which is retained in an animal following administration in the form of sodium sulfate is incorporated in the form of sulfated mucopolysaccharides, especially chondroitin sulfate[3]. Rabbits were given papain 6 and 11 days after receiving S^{35}. Autoradiograms showed a reduction in the S^{35} content of cartilage of papain-injected rabbits, compared with control rabbits. Direct counts of radioactivity of cartilage from papain-injected rabbits determined by Dr. Tsaltas showed approximately 40 per cent less activity than control cartilage. He also

found a rapid rise in the blood and urine levels of S^{35} following papain injection.

Intravenous injections of crude papain into mice, chicks, and hamsters resulted in disappearance of cartilage basophilia. Injection of the plant enzymes bromelin and ficin produces a similar change in mice. Further studies on these enzymes are planned.

Occlusion of the arterial supply of one ear for 15 minutes at the time of injection resulted in protection of that ear against collapse. Progressive loss of rigidity and collapse occurred in isolated rabbit ears excised shortly after the intravenous (femoral vein) injection of crude papain. The rate of collapse in such ears showed a marked temperature dependence. Histologic examination showed changes in cartilage similar to those seen *in vivo*. These results indicate that the active factor is rapidly concentrated in cartilage and that the process is enzymatic in nature.

The daily systemic administration of cortisone, hydrocortisone or prednisilone prevented or greatly delayed recovery of cartilage, as shown by the persistence of ear collapse and the continued histologic abnormalities in cartilage. Prolonged cortisone administration in young rabbits following a single injection of crude papain resulted in virtually complete arrest of enchondral bone formation. These results indicate that cortisone and related steroids interfere with the synthesis or deposition of chondroitin sulfate in cartilage.

In an attempt to find the component in crude papain responsible for the effect on cartilage, two crystalline enzymes prepared from papaya latex[4-6] were tested and the following results were obtained. Crystalline papaya lysozyme was without effect on cartilage. Cysteine activated crystalline papain proteinase in relatively large doses (5 to 10 mg.) produced very slight loss of basophilia of cartilage and did not cause ear collapse. However, when crystalline papain was treated with iodoacetamide or p-chloromercuribenzoate prior to injection, amounts as small as 2 mg. produced total ear collapse and complete loss of cartilage basophilia. It is suggested that these sulfhydryl-blocking agents prevent denaturation of the enzyme in the blood, permitting it to reach cartilage where it is reactivated. This hypothesis is strengthened by observations on factors influencing the rate of collapse in isolated rabbit ears removed shortly after injection into the femoral vein. The skin and subcutaneous tissue of the ears were stripped, exposing the cartilage. Following injection of iodoacetamide inactivated crystalline papain, ears placed in phosphate buffer at pH 7 proceeded to collapse, whereas contralateral ears placed in buffer containing p-chloromercuribenzoate or iodoacetamide failed to collapse. On the other hand, placing ears in buffer containing cysteine and versene greatly increased the rate of collapse. These results indicate that the enzymatic activity in isolated ears depends on SH groups and is consistent with the hypothesis that crystalline papain proteinase is the factor responsible for the effect on cartilage. Following intravenous injection of activated crystalline papain, collapse does not occur in isolated ears. This is consistent with the idea that activated crystalline papain fails to reach cartilage.

These results indicate that crystalline papain is the component in crude papain responsible for the effect on cartilage. Further work on this aspect of the problem is in progress.

The chemical site of action of crystalline papain in cartilage has not been determined, but a consideration of the histologic and chemical findings and known enzymatic action of crystalline papain indicates that it probably attacks the protein moiety of the mucoprotein of cartilage, thus liberating chondroitin sulfate. *In vitro* studies of the effect of crystalline papain on cartilage and the mucoprotein of cartilage are in progress and should clarify this point.

Observations on the Structure and Metabolism of Epiphysial Cartilage

RICHARD H. FOLLIS, JR.

Veterans Administration Central Laboratory for Anatomical Pathology and Research, Armed Forces Institute of Pathology, Washington, D. C.

Tonight I should like to present some observations on the structure of epiphysial cartilage, together with certain changes which may be produced by a number of procedures. In the past the upper epiphysis of the growing rat has been studied extensively, and has provided a great deal of information, for instance in experiments dealing with dietary restrictions of various types, including rickets, endocrine disturbances, etc. The growth activity of this tissue is obviously great, since the entire epiphysial plate may be replaced in two to three days' time.

When fresh stained or unstained cartilage cells are observed, one is impressed by their irregular outlines, a point which was mentioned by Virchow over 100 years ago. When fresh preparations are stained with dilute toluidine blue, the cells take the stain while the matrix generally does not. The response of fixed tissue is different. Cells may be freed from their matrix by treatment with trypsin. Such isolated, yet intact, cells can then be fixed and stained on a slide as one would treat a blood smear. The cytoplasmic detail of such cells is well shown.

Further detail is obtained when one observes thin sections (0.5 micron) of cartilage with the light microscope. Here again the irregular boundaries of the cytoplasm are well shown. Finally, when ultra-thin sections are studied with the electron microscope, intracellular detail and the relation between cytoplasm and matrix are strikingly brought out. These observations have been made in collaboration with Mr. A. J. Tousimis. Briefly, the cell has a prominent endoplasmic reticulum consisting of parallel membranes with dense osmophilic granules attached to them. Sometimes the membranes open out into lake-like vesicular structures. So far, only a few poorly defined mitochondria have been seen. The cytoplasm of the cells extends out into the matrix as finger-like projections, so that the entire cell has a sort of a porcupine appearance. The matrix itself consists of fine unbanded fibers all having approximately the same diameters.

One can then go on to obtain a more precise picture of the chemical structure of cartilage. Its water content is high, approximately 87 per cent. This is well shown by the tremendous collapse which occurs following the injection of crude papain; the epiphysial plate may decrease to one-third of its original width. The inorganic composition is approximately one-quarter of the dry weight. Hence, studies of incinerated sections reveal a prominent ash content in the nucleus, cytoplasm and matrix. Similar distribution is found if microradiographic techniques are applied.

The protein content may be studied by various procedures. DNA is found in the nucleus and there is prominent RNA in the cytoplasm. Small bluish masses interpreted to be mitochondria may be stained with Janus green. Similar aggregates are shown by the Nadi reagent in fresh tissue treated with ethyl carbamate, from which it is concluded that cytochrome oxidase activity is present. The tetrazolium procedure with various substrates indicates the presence of dehydrogenase activity. Alkaline phosphatase may be found in the cytoplasm of hypertrophic cells. Collagen has been identified chemically by the presence of hydroxyproline in isolated cartilage, free of bone and perichondrium, and doubtless is represented by the unbanded fibers seen with the electron microscope.

Of the carbohydrates, glycogen is present in large amounts in the young and mature hypertrophic cells. Alcian blue-staining material is present in the cytoplasm

of the cells and in the matrix as well; such structures are also metachromatic. Both stains probably indicate the presence of chondroitin sulphuric acid (CSA). Although the epiphysial cartilage contains about 0.8 per cent lipid, very little free fat is found in the cells by staining procedures. Neutral fat may appear in abnormal amounts, such as is found when cells are cultivated *in vitro* or in cartilage from rachitic animals.

Certain chemical reagents and enzymes have been utilized to gain a better understanding of the chemical composition of the cells and matrix. If fresh cartilage is treated by materials such as calcium chloride, hyaluronidase, papain, trypsin, etc., then fixed, sectioned and stained in various ways, some idea can be obtained as to the nature of the materials in the matrix. On the basis of such procedures it appears that one can remove the CSA with all of the above reagents, although only one of these, hyaluronidase, depolymerizes CSA. On the other hand, papain and trypsin, which do not act on collagen or CSA, must effect a loss of the latter material because of their digestion of the protein to which it is bound. Utilizing such procedures one gets a little clearer idea of the interrelations of chondroitin sulphuric acid, the protein to which it is complexed, and collagen.

The application of techniques such as these may now be utilized to obtain more information on the pathogenesis of certain experimentally produced disease states in cartilage. Today we are the recipients of "anatomical innovations" just as pathologists were a hundred years ago, when Virchow delivered his lectures on Cellular Pathology.

DISCUSSION

DOMINIC D. DZIEWIATKOWSKI: This has been a most delightful and revealing session to me, and I want to congratulate both speakers on their lucid presentations and on the experimental insight they have demonstrated in those presentations. As I sat listening, particularly to Dr. Follis, I was stimulated, and began to wonder what those pseudopods on the cartilage cells were there for. Is there any function that they have? Do they serve as channels for the excretion or secretion of material which the cell manufactures? I imagine at this time we can do nothing but speculate on that, but I hope sometime in the future someone will tell us what purpose they do serve.

The second thing that came to my mind is that perhaps now we should stop emphasizing the importance of collagen, although to some extent undoubtedly it is important. Instead we should place more emphasis on the mucoproteins and proteins associated with chondroitin sulfate, to which both speakers referred. These two points I think are the most important that were brought out, in addition to the indications that we have certain techniques available by which we may now be able to answer the question as to what role chondroitin sulfate, or the chondroitin sulfate associated with protein, has in the processes of calcification and ossification. In addition to this, I can add very little, and this "little" concerns the background against which both of the presentations of this evening may be viewed. We have made some observations on the possible use of S^{35} as an index of the metabolism of chondroitin sulfate. If one gives S^{35} to an animal, most of it, as Dr. Follis has indicated, is excreted rapidly in the urine and feces; within 24 hours about 80 per cent is eliminated. The remainder is fixed in the tissues which contain polysaccharides.

Within the epiphysial cartilage of a young rat S^{35} accumulates rapidly. Within 24 hours the peak is reached, and thereafter the S^{35} disappears slowly. If one examines these cartilages by autoradiography to determine the localization of the S^{35} within the bones as a whole, the material having been fixed in acidic formalin, the results of autoradiography appear as here (demonstrating on screen). You can see that there is an uneven distribution of S^{35} within the epiphysis. The highest concentration is within the epiphysial plate. The amount of the label increases within these regions rather rapidly; within 24 hours it reaches its peak and then begins to disappear, and to an obvious extent from regions of secondary ossification. In some preparations, that is, in the

humeri from the same animals, if fixed in formalin, saturated with barium hydroxide, the label is removed from the epiphysis, but one does see S^{35} throughout the rest of the bone, the diaphysis, and what is most interesting, as the label disappears from the epiphysial plate region, there is an accumulation of more and more label in the metaphysis. Stained preparations of sections of bones shown previously appear as these do. This is formalin-fixed material stained with toluidin blue.

If one looks at autoradiograms prepared in another fashion, by spreading a thin emulsion over sections, and this emulsion is retained during the subsequent processing, one can see that shortly after the administration of the labeled sulfate most of the label is concentrated within the cell, very little of it is out in the matrix. At eight hours the matrix begins to show more of the label, at 24 hours there is a rather even distribution between cells and matrix, and at 48 hours some of the cells begin to show up nearly free of the isotope. This cellular participation in the synthesis of chondroitin sulfate can be seen better in this preparation, again an autoradiogram, this time of a section of cartilage which first had been incubated *in vitro* in a solution of salts which has S^{35} in it. One can see that the autoradiographic reaction is intracellular, since in this preparation of calf-rib cartilage the chondrocytes are fewer and at greater distances from each other. For comparison of the cellular distribution in such a section, here is a stained preparation.

If you will recall the autoradiograms of the humeri, shown at the beginning of this discussion, there was a progressive loss of S^{35} from the cartilage plate and an accumulation in the trabeculae of the metaphysis. We were interested in trying to see what the nature of the material in the metaphysis might be, and we therefore undertook some chemical analyses. The results of these experiments as shown here indicate that in the epiphyses, diaphyses or metaphyses very little S^{35} labeled sulfate is retained as inorganic sulfate. By isolation of the remainder of the labeled materials from these tissues it was possible to demonstrate that the label in the trabeculae of the metaphysis was associated with chondroitin sulfate, or material like it.

KARL MEYER: I also want to preface my remarks with the statement that we were privileged tonight to hear two very provocative and stimulating papers. The problems dealt with by the speakers, of course, are a challenge to the biochemist as well as to the pathologist. I consider it rather unfortunate that we know so little about the biochemistry of epiphysial cartilage, while hyaline cartilage of trachea and of nasal septum has been studied quite extensively. What holds true for trachea may not be true for epiphysial cartilage. For example, the water content of tracheal cartilage is quite low, in the order of 60 per cent, while Dr. Follis finds in the epiphysial cartilage 87 per cent water. In connective tissue, we believe high water content to be associated with nonsulfated mucopolysaccharides.

We have learned from our investigations on the mucopolysaccharides of connective tissues from different sources that the types of mucopolysaccharides vary in different tissues, both in the types and in their distribution. From the studies of Schubert and his associates, as well as from those of other laboratories, we know that the sulfated mucopolysaccharides occur as complexes of a protein or proteins of still unknown type. It is not known whether or not these proteins are specific for various types of connective tissues or whether they differ with the various types of sulfated mucopolysaccharides. At this stage of our knowledge, it is not possible to give a chemical interpretation of the histological or histochemical data we heard tonight. In our studies on the rather mixed tissue of the long bones of the calf, including the epiphyses, we isolated mucopolysaccharides which are not found in resting hyaline cartilage. Thus we isolated from calf bone in addition to chondroitin sulfate A and C, the only identified mucopolysaccharides of hyaline cartilage, hyaluronic acid, keratosulfate and a large and probably nonhomogeneous chondroitin sulfate fraction, characterized by its incomplete sulfation. Dr. Follis showed in his slides the strong PAS-positive material. I

wonder what the nature of this material is. The isolated acid mucopolysaccharides do not react, or only very slowly, with periodic acid. Another problem arises from the action of papain and testicular hyaluronidase on the tissue slices. The molecular weight of chondroitin sulfate A and C is approximately 45,000 as found especially by Mathews in Chicago. We have to assume that the somewhat rigid rods or coils of this molecule in the native protein complex are bridged by protein. The protein complexes in turn by secondary valences are linked to the collagen fibers forming the cementing substances which bind the fibers into collagen bundles. When papain acts on the protein complexes, we assume that it breaks some peptide bonds of the protein. The question then arises whether the peptides thus formed are still linked to chondroitin sulfate. Conversely when hyaluronidase acts on the complexes, we would expect that the protein is left still attached to an oligosaccharide.

THEODORE TSALTAS: I would like to make some comments about the work Dr. McCluskey mentioned tonight. We have been doing some chemical determinations, on experimental animals similar to the ones Dr. McCluskey mentioned. I think some of the determinations were performed on the same animals. As Dr. McCluskey mentioned, many of our experiments were also performed 24 hours after the injection of papain. We had animals as controls and animals sacrificed 24 hours after the injection of papain. We noted a decrease of mucochondroitin sulfate of about 40 per cent, and also the S^{35} content of such mucochondroitin sulfate was 40 per cent less. Dr. McCluskey showed some pictures where there was some basophilic material in the tissues surrounding the cartilage, and the question was asked, where did that material go? We have some evidence that these sulfur-containing compounds are circulating in the blood in various forms. We isolated materials of various molecular weights, organic material that cannot be precipitated with trichloroacetic acid, and organic material that can be precipitated with trichloroacetic acid, as well as inorganic S containing materials. All these three classes showed increased concentration in the blood stream after the injection of papain, and some S^{35} was excreted in the urine. The increase was about 50 per cent over the controls for a 24 hour period. These experiments were performed 24 hours after the injection of papain. We did a series of experiments in which the animals were sacrificed every 4 hours up to 72 hours after the injection of papain. The maximum effect of the injection of papain occurred 12 hours after the injection. It lasted at about the same level for another 12 hours, that is, 24 hours from the injection of papain. The difference here is that Dr. McCluskey has observed that the changes persist for several days, while from our chemical determinations we found that the amount of chondroitin sulfate was almost at the normal level at 60 hours after the injection of papain. Also the amount of S^{35} in the blood stream reached the maximum 12 hours after the injection of papain and started decreasing steadily until it reached a low point at about 60 hours after the injection of papain. There is a point at which we do not understand definitely what is happening, that is, the S^{35} returns to the cartilage in some form that we do not know, but when we measure the S^{35} activity in cartilage 60 hours after the injection of papain, there is definitely S^{35} in larger amounts than were there 12 to 24 hours after the injection of papain.

A very interesting change was found in the $\frac{\text{nitrogen}}{\text{hexosamine}}$ ratio of the isolated mucochondroitin sulfate. This ratio changed by virtue of increased N_2 and decreased hexosamine. This change reached a maximum 12 to 24 hours after the injection of papain and returned to normal levels approximately 60 hours from the time of injection. This change in ratio can possibly give an indication of what happens in the molecule of mucochondroitin sulfate. It seems to us that papain breaks the molecule in such a fashion as to liberate hexosamine in larger amounts than peptides resulting in the ratio changes and the difference between control and treated animals. I cannot say that we are 100 per cent sure of this, be-

cause our material has to be purified, and the small remnants of cartilage have to be removed by hydrolysis before we have 100 per cent evidence, but the method by which we extracted the chondroitin sulfate allows us to be sure that something like this might have been happening.

Also I should like to add a word about the possibility of having edema in the tissue surrounding the cartilage: from our experience the ratio of the wet and dried cartilage in treated and control animals, as far as the weight was concerned, was the same: 3 to 1. As the wet cartilage and the papain-treated cartilage had exactly the same weight ratio, there is no possibility that the accumulation of water might have changed the properties.

I should like to make a comment about the staining methods mentioned by Dr. Follis. In some experiments that we did over the last two months we have been able to fractionate Sudan II (or Oil Red "O"), and we have found four compounds. One component stained fatty acids; two other components stained lipids, while a fourth stained proteins, so I do not know what those materials presented tonight might consist of, when stained with the mixture of these four components.

ALBERT SOBEL: I should like to compliment the contributors to this session for being most stimulating. I should like to ask Dr. Follis two questions: First, did he find any particular difference between preosseous and ossifying cartilage matrix? Second, does he think that alcian blue and toluidine blue stain two different substances, or different modifications of the same substance?

I should like to ask Dr. Dziewiatkowski: Is it possible that barium interferes with the metachromatic reaction of chondroitin sulfate?

DOMINIC D. DZIEWIATKOWSKI: It is possible that barium ions could interfere and mask the metachromatic reaction of chondroitin sulfate. In our preparations of cartilage fixed in formalin saturated with barium hydroxide, however, we feel that chondroitin sulfate is no longer present. This is supported by the fact that during the process of fixation S^{35} is lost from the cartilage.

KARL MEYER: I should like to ask whether changes have been observed in tissues other than cartilage. I believe Dr. McCluskey said there were no changes in other tissues following papain injection. I wonder whether studies have been carried out on the binding of papain by tissues other than cartilage. I have specifically in mind aorta in which the chief mucopolysaccharide fraction is chondroitin sulfate A, apparently identical with that of cartilage.

MARTIN BURGER: It was gratifying to learn that Dr. Follis observed that the collagen in the matrix was not banded. There seems to be some controversy about the calcifiability of banded and unbanded collagen. The M. I. T. group in Boston[7] believe that only 640 A banded fibrils will calcify *in vitro*. We in our laboratory have repeatedly obtained *in vitro* calcification of chondroitin sulfate precipitated acid soluble collagen and this material is not banded, according to Fitton Jackson and Randall[8]. I just wanted to point this out for further comment by Dr. Follis.

ROBERT T. McCLUSKEY: In answer to Dr. Meyer's question, we have no evidence that papain has any effect on the mucopolysaccharides of the aorta or of other connective tissue and up to the present time we have no evidence that papain is concentrated in any site except cartilage. We may be able to find that out by using *in vitro* techniques comparable to that of the isolated rabbit's ear.

THEODORE TSALTAS: Dr. McCluskey had given me a couple of corneas and aortas of his animals, and I had taken some of my own, and when we did determinations on these materials (there were very few animals, I do not claim this will be of any particular value, except as an initial investigation) we found a decrease in the amount of S^{35} in the cornea and aorta of the treated rabbits. The decrease of S^{35} was not as striking as in the cartilage, but that

is as far as we went; I have not done any further work on it.

R. H. FOLLIS, JR.: To answer Dr. Sobel, the answer is, as far as calcification goes, "no". That is, there is nothing one sees in the calcifying area that is different from any others.

I do not know what the collagen fibers, whether banded or not, have to do with the calcification mechanism. The fact that fibers in cartilage do not show periodicity would make the hypothesis of Glimcher and associates open to some question. What the calcification mechanism is continues to be a mystery, to me at least.

As far as the question that Dr. Sobel asked about alcian blue and toluidine blue, this has been somewhat hard to interpret. The alcian blue apparently stains chondroitin sulfate; toluidine blue does also, but apparently stains something else; at least, that is our interpretation. I might add that we have applied a lot of other things to cartilage, which I did not show you; diastase and pancreatin work in the expected fashion.

I wish Dr. Meyer had drawn the little picture tonight which he drew for me yesterday and which explains this very lucidly. It made things very understandable and I think helps explain the results one gets *in vivo* and *in vitro*. The CSA molecules, which are long structures, may be bound together end to end by molecules of protein. These then may in some fashion be bound to collagen molecules, which are claimed to be 3000 A in length and 12 or 13 A in diameter. If one applies trypsin or papain, that is, proteolytic enzymes, of which the former does not act on collagen, and papain, which as far as I know, does not either, we break up the protein and doubtless liberate whole molecules of chondroitin sulfate, perhaps bound to the degradation product of this protein. If you incubate the tissue with hyaluronidase, you break up the CSA molecule itself and may at the same time liberate protein, perhaps that which was attached to the collagen molecules, so that you get rid of the alcian blue staining and some of the metachromasia. The concept of Dr. Meyer was extremely helpful to me and perhaps may be to you.

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RESEARCH CONTRIBUTIONS TO CLINICAL PRACTICE

PANEL MEETING — 3:30 P.M.

Monday October 13

THE DIAGNOSIS AND MANAGEMENT OF CEREBRAL VASCULAR DISEASES

Chairman: IRVING S. WRIGHT, *Cornell University Medical College*

LECTURES — 8:30 P.M.

STUDIES OF CONTRACTILE PROTEINS OF MUSCLE

ANDREW G. SZENT-GYORGYI, *Institute for Muscle Research*

THE METABOLISM OF THE ERYTHROCYTE

IRVING M. LONDON, *Albert Einstein College of Medicine*

STUDIES OF THE LE CELL AND THE LE FACTORS

HENRY G. KUNKEL, *The Rockefeller Institute for Medical Research*

PANEL MEETING — 3:30 P.M.

Tuesday October 14

INFLUENZA AND UPPER RESPIRATORY INFECTIONS

Chairman: WALSH McDERMOTT, *Cornell University Medical College*

LECTURES — 8:30 P.M.

HEREDITARY ASPECTS OF DISEASE

BARTON CHILDS, *The Johns Hopkins University School of Medicine*

CONGENITAL DISEASES OF BLOOD PROTEINS

CHARLES A. JANEWAY, *Harvard Medical School*

HEREDITARY DISEASES OF CONNECTIVE TISSUE

VICTOR A. McKUSICK, *The Johns Hopkins University School of Medicine*

PANEL MEETING — 3:30 P.M.

Wednesday October 15

GLOMERULONEPHRITIS AND PYELONEPHRITIS

Chairman: WILLIAM GOLDRING, *New York University College of Medicine*

LECTURES — 8:30 P.M.

SOME MECHANISMS OF BACTERICIDAL CHEMOTHERAPEUTIC ACTION

BERNARD D. DAVIS, *Harvard Medical School*

(Program continued on next page)

THE NEW YORK ACADEMY OF MEDICINE

SECOND ANNUAL POSTGRADUATE WEEK

OCTOBER 13 to 17, 1958

RESEARCH CONTRIBUTIONS TO CLINICAL PRACTICE

LECTURES — 8:30 P.M. (continued)

Wednesday October 15 *(continued)*

OBSERVATIONS ON THE NATURE OF STAPHYLOCOCCAL INFECTIONS
DAVID E. ROGERS, *Cornell University Medical College*

THE CONTROL OF STAPHYLOCOCCAL SEPSIS
CARL W. WALTER, *Harvard Medical School*

PANEL MEETING — 3:30 P.M.

Thursday October 16

POTASSIUM THERAPY
Chairman: SAUL J. FARBER, *New York University College of Medicine*

LECTURES — 8:30 P.M.

HEPATIC CIRCULATORY PHYSIOLOGY
STANLEY E. BRADLEY, *College of Physicians and Surgeons, Columbia University*

JAUNDICE AND BILIRUBIN METABOLISM
RUDI SCHMID, *Harvard Medical School*

MANAGEMENT OF PORTAL HYPERTENSION
ARTHUR B. VOORHEES, *Jr., College of Physicians and Surgeons, Columbia University*

PANEL MEETING — 3:30 P.M.

Friday October 17

THE RADIATION HAZARD
Chairman: J. E. RALL, *National Institutes of Health*

LECTURES — 8:30 P.M.

THE FATE OF SODIUM AND WATER IN THE RENAL TUBULES
HOMER W. SMITH, Sc.D., *New York University College of Medicine*

MECHANISMS OF RENAL TUBULAR TRANSPORT
JOHN V. TAGGART, *College of Physicians and Surgeons, Columbia University*

ELECTRON MICROSCOPY OF THE KIDNEY IN NORMAL AND DISEASED STATES
JOHANNES A. G. RHODIN, *New York University College of Medicine*

SCIENTIFIC EXHIBIT

The Scientific Exhibit will open officially at 11 a.m. WEDNESDAY, OCTOBER 8, 1958 and be open daily 10 a.m. to 10 p.m. through October 17 except Saturday and Sunday, October 11 and 12.

COURSE FOR GENERAL PRACTITIONERS

A three-session course, **without fee**, for General Practitioners has been arranged by the Committee on Medical Education of The New York Academy of Medicine and is approved by the New York State Chapter of the American Academy of General Practice for its members for 5 hours of credit, Category I. This course will be given at the Academy on the dates and time listed below.

PRACTICAL APPLICATIONS OF ELECTROLYTE AND FLUID BALANCE

9:00-10:30 p.m.
Thursday
October 23, 1958

Part I: IN MANAGEMENT OF CARDIAC DISEASE

Chairman—E. HUGH LUCKEY, *The New York Hospital-Cornell Medical Center*

9:00-10:30 p.m.
Thursday
November 20, 1958

Part II: IN MANAGEMENT OF RENAL AND LIVER DISEASE

Chairman—NORMAN DEANE, *New York University-Bellevue Medical Center*

9:00-10:30 p.m.
Thursday
December 18, 1958

Part III: IN MANAGEMENT OF SURGICAL CONDITIONS

Chairman—HENRY T. RANDALL, *Memorial Center for Cancer and Allied Diseases*

Advance registration is required

All inquiries and requests concerning registration should be addressed to:

Secretary, Committee on Medical Education
THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

MONTHLY PANEL MEETINGS FOR THE GENERAL PHYSICIAN

Seventh Series — 1958-1959

(Please note: For the coming academic year these meetings will be held on the SECOND FRIDAY of the month, November 1958 through April 1959 at 4:00 p.m., in Room 20 at the Academy.)

FRIDAY November 14 1958	THE USE AND ABUSE OF TRANQUILIZERS *Moderator:* JOHN M. COTTON
FRIDAY December 12 1958	CURRENT THERAPY OF PULMONARY TUBERCULOSIS *Moderator:* JOHN H. MCCLEMENT
FRIDAY January 9 1959	ADVANCES IN THE MANAGEMENT OF LYMPHOMAS *Moderator:* CLAUDE E. FORKNER
FRIDAY February 13 1959	USE OF STEROIDS IN RHEUMATIC DISEASES *Moderator:* CHARLES RAGAN
FRIDAY March 13 1959	THE USE OF CHLOROTHIAZIDE AND OTHER DIURETIC AGENTS *Moderator:* JOHN H. LARAGH
FRIDAY April 10 1959	PROPHYLACTIC USE OF ANTIBIOTICS *Moderator:* PERRIN H. LONG

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The October 2, 9 and 16 programmes have been postponed due to unavoidable alterations in Radio Station WNYC schedules.

Oct. 23—MANAGEMENT OF THE PREGNANT DIABETIC (panel)—Irving Graef, moderator, *New York University, Post-Graduate Medical School;* Priscilla White, William P. Given, Henry Dolger, Walter S. Jones, Edmund L. Shlevin, Alvin J. B. Tillman. (Section I)

Oct. 30—MANAGEMENT OF THE PREGNANT DIABETIC (panel)—(Section II)

DATA ON INTERNATIONAL CONGRESSES REQUESTED BY LIBRARY

Fellows are reminded that the Library is eager to acquire the publications of all international congresses, their programs, bulletins, proceedings, reports. Since these are often hard to find, it would help a great deal if Fellows attending such congresses would turn over to the Library any such papers as they themselves do not wish to keep. Such thoughtfulness would be deeply appreciated.

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FINNERTY, F. A., Buchholz, J. H. and Tuckman, J.: J.A.M.A. **166**:141, Jan. 11, 1958.

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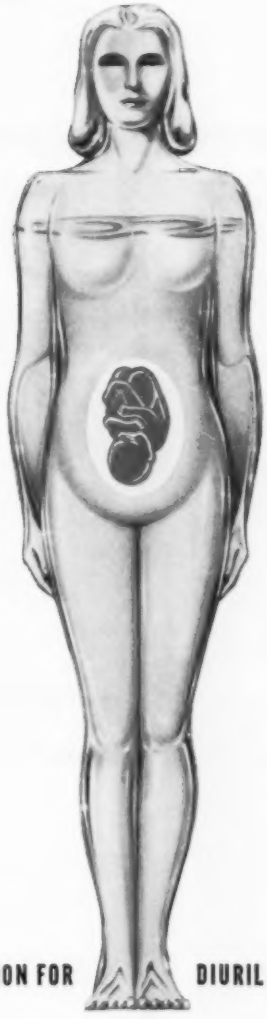

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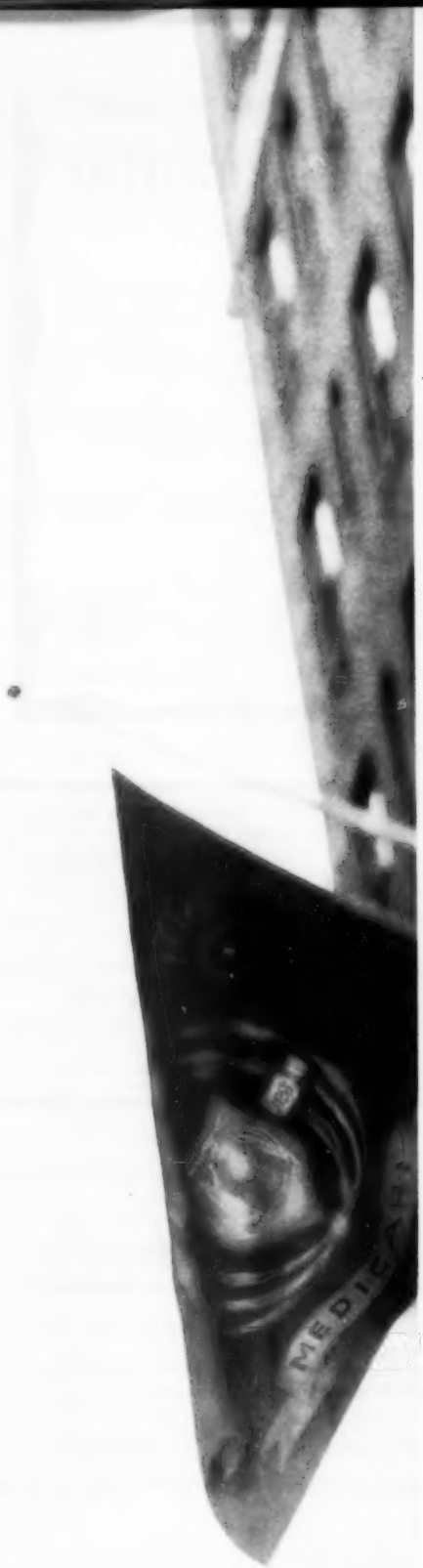

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1. Kety, S. S.: A medical regimen for benign rectal disorders, *GP* 10:75, Nov., 1954.

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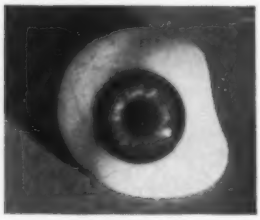

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FORD, R. V., Rochelle, J.B.III, Handley, C. A., Moyer, J. H. and Spurr, C. L.: J.A.M.A. **166**:129, Jan. 11, 1958.

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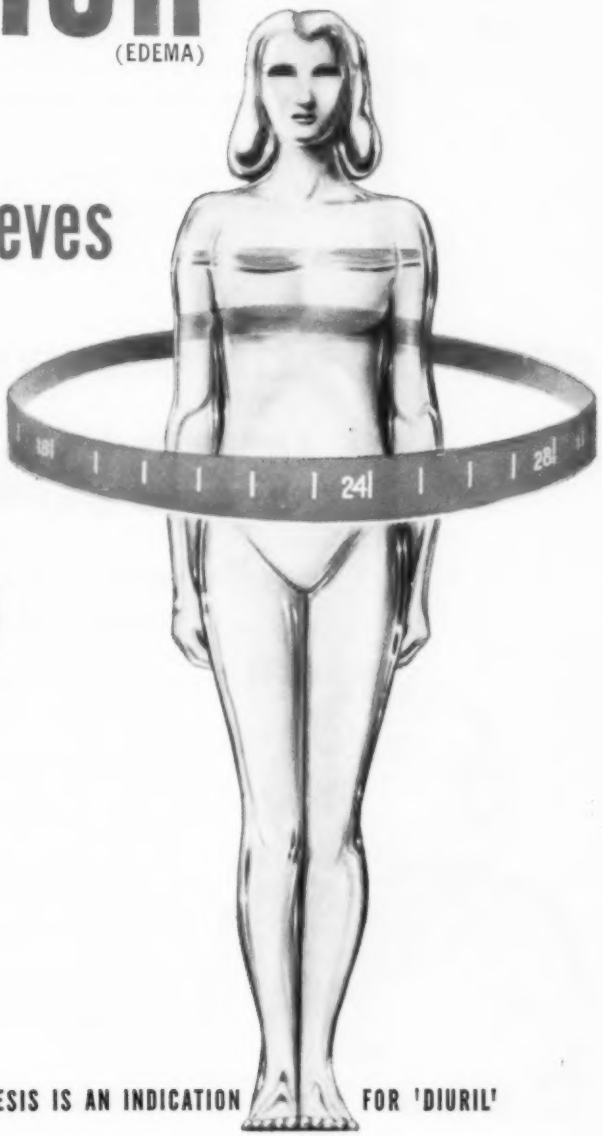

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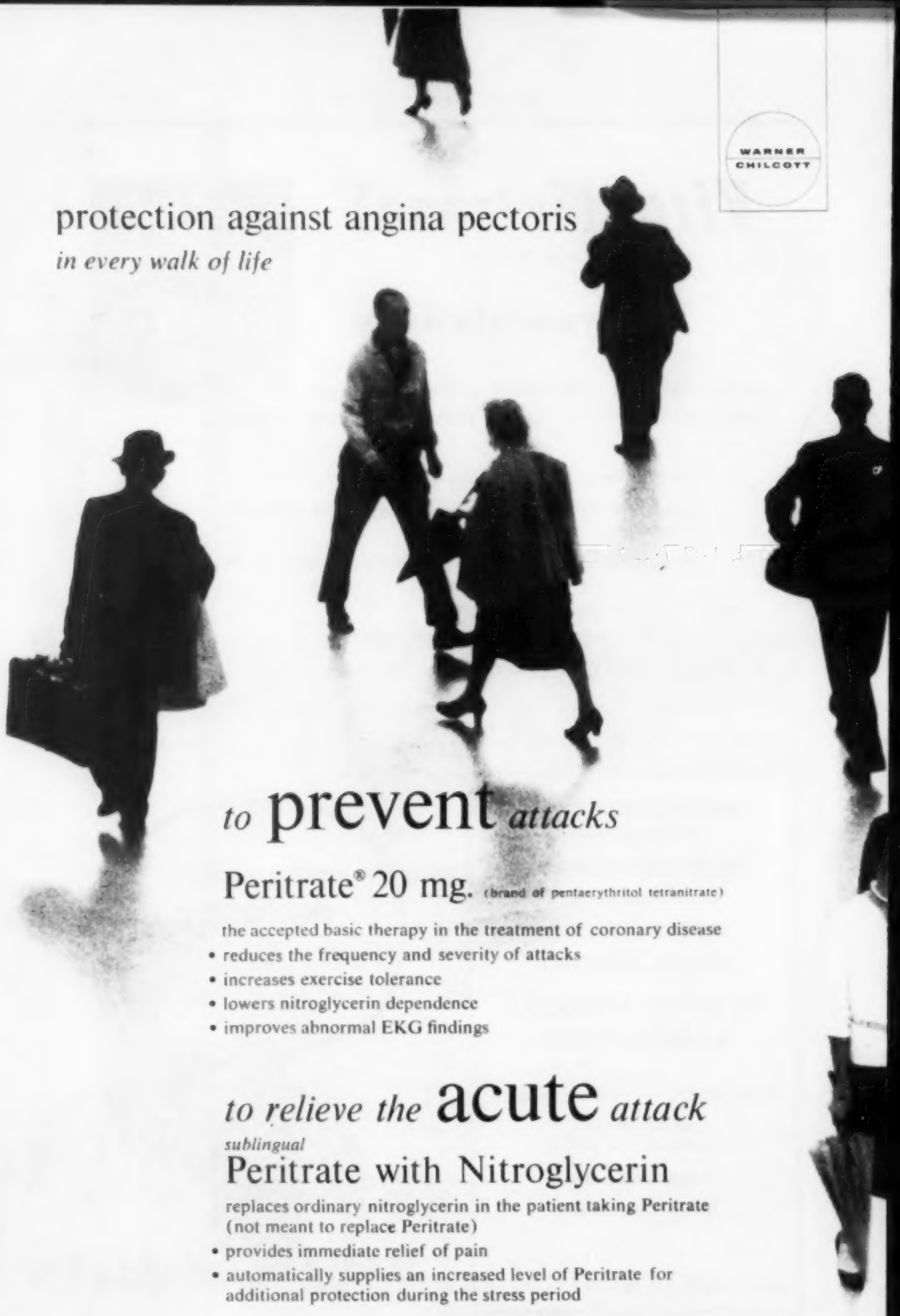

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(1) Kleitsmer, M. S., Jr.: J. Louisiana M. Soc. 109:329, 1956. (2) Rives, J. A.: Am. J. Gastroenterol. 20:441, 1953. (3) Kleitsmer, M. S., Jr.: Clin. Proc. 3:19, 1957.

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